1 NAME OF THE MEDICINAL PRODUCT

TRAJENTA DUO 2.5 mg/500 mg

TRAJENTA DUO 2.5 mg/850 mg

TRAJENTA DUO 2.5 mg/1,000 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Linagliptin 2.5 mg and 500/850/1000 mg Metformin.

For the full list of excipients, see section "Description".

3 PHARMACEUTICAL FORM

Film coated tablets.

WARNING: RISK OF LACTIC ACIDOSIS

Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL *[see Warnings and Precautions (8.1)].*

Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.

Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the full prescribing information *[see Dosage and Administration (5.2), Contraindications (7), Warnings and Precautions (8.1), Drug Interactions (10.1), and Use in Specific Populations (11.6, 11.7)].*

If metformin-associated lactic acidosis is suspected, immediately discontinue Trajenta Duo and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended *[see Warnings and Precautions (8.1)].*

4 INDICATIONS AND USAGE

4.1 Indication

TRAJENTA DUO is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate *[see Dosage and Administration (5.1) and Clinical Studies (16.1)]*.

4.2 Important Limitations of Use

TRAJENTA DUO should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings. TRAJENTA DUO has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at an increased risk for the development of pancreatitis while using TRAJENTA DUO *[see Warnings and Precautions (8.2)]*.

5 DOSAGE AND ADMINISTRATION

5.1 DosageAdults with normal renal function (glomerular filtration rate [GFR] ≥ 90 ml/min)

The dosage of TRAJENTA DUO should be individualized on the basis of both effectiveness and tolerability, while not exceeding the maximum recommended dose of 2.5 mg linagliptin/1000 mg metformin hydrochloride twice daily. TRAJENTA DUO should be given twice daily with meals. Dose escalation should be gradual to reduce the gastrointestinal (GI) side effects associated with metformin use. For available dosage forms and strengths *[*see *Dosage Forms and Strengths (6)]*.

Recommended starting dose:

- In patients currently not treated with metformin, initiate treatment with 2.5 mg linagliptin/500 mg metformin hydrochloride twice daily
- In patients already treated with metformin, start with 2.5 mg linagliptin and the current dose of metformin taken at each of the two daily meals (e.g., a patient on metformin 1000 mg twice daily would be started on 2.5 mg linagliptin/1000 mg metformin hydrochloride twice daily with meals).
- Patients already treated with linagliptin and metformin individual components may be switched to TRAJENTA DUO containing the same doses of each component.

No studies have been performed specifically examining the safety and efficacy of TRAJENTA DUO in patients previously treated with other oral antihyperglycemic agents and switched to TRAJENTA DUO. Any change in therapy of type 2 diabetes mellitus should be undertaken with care and appropriate monitoring as changes in glycemic control can occur.

5.2 Recommended Dosing in Renal Impairment

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at 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.
The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis *[see Warnings and Precautions (8.1)]* should be reviewed before considering initiation of metformin in patients with GFR<60 ml/min.
If no adequate strength of Trajenta Duo is available, individual monocomponents should be used instead of the fixed dose combination.

GFR ml/min	metformin	linagliptin
60-89	Maximum daily dose is 2550 mg Dose reduction may be considered in relation to declining renal function.	No dose adjustment
45-59	Maximum daily dose is 2000 mg The starting dose is at most half of the maximum dose.	No dose adjustment
30-44	Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.	No dose adjustment
<30	Metformin is contraindicated	No dose adjustment

6 DOSAGE FORMS AND STRENGTHS

TRAJENTA DUO is a combination of linagliptin and metformin HCl. TRAJENTA DUO tablets are available in the following dosage forms and strengths:

- 2.5 mg linagliptin/500 mg metformin HCl tablets are light yellow, oval, biconvex tablets debossed with “D2/500” on one side and the Boehringer Ingelheim logo on the other side
- 2.5 mg linagliptin/850 mg metformin HCl tablets are light orange, oval, biconvex tablets debossed with “D2/850” on one side and the Boehringer Ingelheim logo on the other side
- 2.5 mg linagliptin/1000 mg metformin HCl tablets are light pink, oval, biconvex tablets debossed with “D2/1000” on one side and the Boehringer Ingelheim logo on the other side

7 CONTRAINDICATIONS

TRAJENTA DUO is contraindicated in patients with:

- Severe renal impairment eGFR below 30 mL/min/1.73 m2) [see *Warnings and Precautions (8.1)*]
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. *[see Warnings and Precautions (8.1)]*
- Hypersensitivity to linagliptin, metformin, or any excipients in Trajenta Duo, reactions such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity have occurred with linagliptin [see *Warnings and Precautions (8.5), Adverse Reactions (9.1) and Description (13)]*

8 WARNINGS AND PRECAUTIONS

8.1 Lactic Acidosis

Metformin

There have been postmarketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate pyruvate ratio; metformin plasma levels generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of TRAJENTA DUO. In TRAJENTA DUO-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable, with clearance of up to 170 mL/min under good hemodynamic conditions) Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue TRAJENTA DUO and report these symptoms to their healthcare provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

Renal Impairment: The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include *[see Dosage and Administration (5.2) and Clinical Pharmacology (14.3)]:*

- Before initiating TRAJENTA DUO, obtain an estimated glomerular filtration rate (eGFR).
- TRAJENTA DUO is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2 *[see Contraindications (7)].*
- Initiation of TRAJENTA DUO is not recommended in patients with eGFR between 30 − 45 mL/min/1.73 m^2.
- Obtain an eGFR at least annually in all patients taking TRAJENTA DUO. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.
- In patients taking TRAJENTA DUO whose eGFR later falls below 45 mL/min/1.73 m^2, assess the benefit and risk of continuing therapy

Drug Interactions: The concomitant use of TRAJENTA DUO with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation *[see Drug Interactions (8.1)]*. Therefore, consider more frequent monitoring of patients.

Age 65 or Greater: The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients *[see Use in Specific Populations (11.5)]*.

Radiological studies and surgical procedures:
Radiologic studies involving the use of intravascular iodinated contrast materials (e.g., intravenous urogram, intravenous cholangiography, angiography, and computed tomography) can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, TRAJENTA-DUO should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been confirmed to be stable.

Surgery and Other Procedures: Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. TRAJENTA DUO should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States: Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue TRAJENTA DUO.

Excessive Alcohol Intake: Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving TRAJENTA DUO.

Hepatic Impairment: Patients with hepatic impairment have developed cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of TRAJENTA DUO in patients with clinical or laboratory evidence of hepatic disease.

8.2 Pancreatitis
Acute pancreatitis, including fatal pancreatitis, has been reported in patients treated with linagliptin. In the CARMELINA trial *[see Clinical Studies (14.2)]*, acute pancreatitis was reported in 9 (0.3%) patients treated with linagliptin and in 5 (0.1%) patients treated with placebo. Two patients treated with linagliptin in the CARMELINA trial had acute pancreatitis with a fatal outcome.

There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis, in patients treated with linagliptin. Take careful notice of potential signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue TRAJENTA DUO and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using TRAJENTA DUO.

8.3 Heart Failure

An association between DPP-4 inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease.

Consider the risks and benefits of TRAJENTA DUO prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of TRAJENTA DUO.

8.4 Use with Medications Known to Cause Hypoglycemia

Insulin secretagogues and insulin are known to cause hypoglycemia. The use of linagliptin in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin was associated with a higher rate of hypoglycemia compared with placebo in clinical trials *[see Adverse Reactions (9.1)]*. Metformin may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with TRAJENTA DUO *[see Drug Interactions (10.3)]*.

8.5 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with linagliptin (one of the components of TRAJENTA DUO). These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred predominantly within the first 3 months after initiation of treatment with linagliptin, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue TRAJENTA DUO, assess for other potential causes for the event, and institute alternative treatment for diabetes.

Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema to another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with TRAJENTA DUO.

8.6 Vitamin B_{12} Levels

In controlled, 29-week clinical trials of metformin, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of metformin-treated patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, may be associated with anemia or neurologic manifestations. This risk may be more relevant to patients receiving long-term treatment with metformin, and adverse hematologic and neurologic reactions have been reported postmarketing. The decrease in vitamin B_{12} levels appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis and routine serum vitamin B12 measurement at 2- to 3-year intervals is advised in patients on TRAJENTA DUO and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels.

8.7 Severe and Disabling Arthralgia

There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

8.8 Bullous Pemphigoid

Bullous pemphigoid was reported in 7 (0.2%) patients treated with linagliptin compared to none in patients treated with placebo in the CARMELINA trial *[see Clinical Studies (16.2)]*, and 3 of these patients were hospitalized due to bullous pemphigoid. Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving TRAJENTA DUO. If bullous pemphigoid is suspected, TRAJENTA DUO should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

9 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Lactic Acidosis *[see Warnings and Precautions (8.1)]*
- Pancreatitis *[see Warnings and Precautions (8.2)]*
- Heart Failure *[see Warnings and Precautions (8.3)]*
- Use with Medications Known to Cause Hypoglycemia *[see Warnings and Precautions (8.4)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (8.5)]*

- Vitamin B12 Levels *[see Warnings and Precautions (8.6)]*
- Severe and Disabling Arthralgia *[see Warnings and Precautions (8.7)]*
- Bullous Pemphigoid *[see Warnings and Precautions (8.8)]*

9.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Linagliptin/Metformin

The safety of concomitantly administered linagliptin (daily dose 5 mg) and metformin (mean daily dose of approximately 1800 mg) has been evaluated in 2816 patients with type 2 diabetes mellitus treated for ≥12 weeks in clinical trials.

Three placebo-controlled studies with linagliptin + metformin were conducted: 2 studies were 24 weeks in duration, 1 study was 12 weeks in duration. In the 3 placebo-controlled clinical studies, adverse reactions which occurred in ≥5% of patients receiving linagliptin + metformin (n=875) and were more common than in patients given placebo + metformin (n=539) included nasopharyngitis (5.7% vs 4.3%).

In a 24-week factorial design study, adverse reactions reported in ≥5% of patients receiving linagliptin + metformin and were more common than in patients given placebo are shown in Table 1.

Table 1 Adverse Reactions Reported in ≥5% of Patients Treated with Linagliptin + Metformin and Greater than with Placebo in a 24-week Factorial-Design Study

	Placebo n=72	**Linagliptin Monotherapy n=142**	**Metformin Monotherapy n=291**	**Combination of Linagliptin with Metformin n=286**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Nasopharyngitis	1 (1.4)	8 (5.6)	8 (2.7)	18 (6.3)
Diarrhea	2 (2.8)	5 (3.5)	11 (3.8)	18 (6.3)

Other adverse reactions reported in clinical studies with treatment of linagliptin + metformin were hypersensitivity (e.g., urticaria, angioedema, or bronchial hyperreactivity), cough, decreased appetite, nausea, vomiting, pruritus, and pancreatitis.

Linagliptin
Adverse reactions reported in ≥2% of patients treated with linagliptin 5mg and more commonly than in patients treated with placebo included: nasopharyngitis (7.0% vs 6.1%), diarrhea (3.3% vs 3.0%), and cough (2.1% vs 1.4%).

Rates for other adverse reactions for linagliptin 5 mg vs placebo when linagliptin was used in combination with specific anti-diabetic agents were: urinary tract infection (3.1% vs 0%) and hypertriglyceridemia (2.4% vs 0%) when linagliptin was used as add-on to sulfonylurea; hyperlipidemia (2.7% vs 0.8%) and weight increased (2.3% vs 0.8%) when linagliptin was used as add-on to pioglitazone; and constipation (2.1% vs 1%) when linagliptin was used as add-on to basal insulin therapy.

Other adverse reactions reported in clinical studies with treatment of linagliptin monotherapy were hypersensitivity (e.g., urticaria, angioedema, localized skin exfoliation, or bronchial hyperreactivity) and myalgia. In the clinical trial program, pancreatitis was reported in 15.2 cases per 10,000 patient year exposure while being treated with linagliptin compared with 3.7 cases per 10,000 patient year exposure while being treated with comparator (placebo and active comparator, sulfonylurea). Three additional cases of pancreatitis were reported following the last administered dose of linagliptin.

Metformin
The most common adverse reactions due to initiation of metformin are diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache.

Hypoglycemia
Linagliptin/Metformin
In a 24-week factorial design study, hypoglycemia was reported in 4 (1.4%) of 286 subjects treated with linagliptin + metformin, 6 (2.1%) of 291 subjects treated with metformin, and 1 (1.4%) of 72 subjects treated with placebo. The incidence of hypoglycemia with plasma glucose <54 mg/dL was 8.1% in the linagliptin group (N=792) compared to 5.3% in the placebo group (N=263) when administered in combination with metformin and sulfonylurea in a 24-week study.

Linagliptin
The incidence of severe hypoglycemia (requiring assistance) was 1.7% in the linagliptin group (N=631) compared to 1.1% in the placebo group (N=630) when administered in combination with basal insulin in a 52 week study.

Laboratory Tests
Linagliptin
Increase in Uric Acid: Changes in laboratory values that occurred more frequently in the linagliptin group and ≥1% more than in the placebo group were increases in uric acid (1.3% in the placebo group, 2.7% in the linagliptin group).

Increase in Lipase: In a placebo-controlled clinical trial with linagliptin in type 2 diabetes mellitus patients with micro- or macroalbuminuria, a mean increase of 30% in lipase concentrations from baseline to 24 weeks was observed in the linagliptin arm compared to a mean decrease of 2% in the placebo arm. Lipase levels above 3 times upper limit of normal were seen in 8.2% compared to 1.7% patients in the linagliptin and placebo arms, respectively.

Increase in Amylase: In a cardiovascular safety study comparing linagliptin versus glimepiride in patients with type 2 diabetes mellitus, amylase levels above 3 times upper limit of normal were seen in 1.0% compared to 0.5% of patients in the linagliptin and glimepiride arms, respectively.

The clinical significance of elevations in lipase and amylase with linagliptin is unknown in the absence of potential signs and symptoms of pancreatitis *[see Warnings and Precautions (5.2)]*.

Metformin

Decrease in Vitamin B_{12} Absorption: Treatment with metformin has been associated with a decrease in vitamin B_{12} absorption which may result in clinically significant vitamin B_{12} deficiency (e.g., megaloblastic anemia) *[see Warnings and Precautions (8.6)]*.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

9.2 Postmarketing Experience

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

Linagliptin

- Acute pancreatitis, including fatal pancreatitis *[see Indications and Usage (4)*
- Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions
- Severe and disabling arthralgia
- Rash
- Bullous pemphigoid
- Mouth ulceration, stomatitis
- Rhabdomyolysis

Metformin

- Cholestatic, hepatocellular, and mixed hepatocellular liver injury

10 DRUG INTERACTIONS

10.1 Drug Interactions with Metformin

Carbonic Anhydrase Inhibitors
Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with TRAJENTA DUO may increase the risk of lactic acidosis Consider more frequent monitoring of these patients *[see Warnings and Precautions (8.1) and Clinical Pharmacology (14.3)]*.

Drugs that Reduce Metformin Clearance
Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis *[see Clinical Pharmacology (14.3)]*. Consider the benefits and risks of concomitant use.

Alcohol
Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving TRAJENTA DUO.

10.2 Drug Interactions With Linagliptin

Inducers of P-glycoprotein and CYP3A4 Enzymes
Rifampin decreased linagliptin exposure, suggesting that the efficacy of linagliptin may be reduced when administered in combination with a strong P-gp inducer or CYP 3A4 inducer. As TRAJENTA DUO is a fixed-dose combination of linagliptin and metformin, use of alternative treatments (not containing linagliptin) is strongly recommended when concomitant treatment with a strong P-gp or CYP 3A4 inducer is necessary *[see Clinical Pharmacology (14.3)]*.

10.3 Insulin Secretagogues or Insulin

Co-administration of TRAJENTA DUO with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia *[see Warnings and Precautions (8.4)]*.

10.4 Drugs Affecting Glycemic Control

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving TRAJENTA DUO, the patient should be closely observed to maintain adequate glycemic control *[see Clinical*

Pharmacology (14.3)]. When such drugs are withdrawn from a patient receiving TRAJENTA DUO, the patient should be observed closely for hypoglycemia.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk Summary

The limited data with TRAJENTA DUO and linagliptin use in pregnant women are not sufficient to inform a TRAJENTA DUO-associated or linagliptin-associated risk for major birth defects and miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk *[see Data]*. 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 the combination of linagliptin and metformin 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, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia- related morbidity.

Data

Human Data

Published data from post-marketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during pregnancy. However, these studies cannot definitely establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Animal Data

Linagliptin and metformin, the components of TRAJENTA DUO, were coadministered to pregnant Wistar Han rats during the period of organogenesis. No adverse developmental outcome was

observed at doses similar to the maximum recommended clinical dose, based on exposure. At higher doses associated with maternal toxicity, the metformin component of the combination was associated with an increased incidence of fetal rib and scapula malformations at ≥ 9-times a 2000 mg clinical dose, based on exposure.

Linagliptin
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 and 150 mg/kg, respectively. These doses represent approximately 943 times (rats) and 1943 times (rabbits) the 5 mg 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 5 mg clinical dose, based on exposure.

Metformin Hydrochloride
Metformin hydrochloride did not cause adverse developmental effects when administered to pregnant rabbits up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of approximately 6-times a clinical dose of 2000 mg, based on body surface area.

11.2 Lactation
Risk Summary
There is no information regarding the presence of TRAJENTA DUO or linagliptin in human milk, the effects on the breastfed infant, or the effects on milk production. However, linagliptin is present in rat milk. Limited published studies report that metformin is present in human milk *[see Data]*. However, there is insufficient information to determine the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRAJENTA DUO and any potential adverse effects on the breastfed child from TRAJENTA DUO or from the underlying maternal condition.

Data
Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

11.3 Females and Males of Reproductive Potential
Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

11.4 Pediatric Use

Safety and effectiveness of TRAJENTA DUO in pediatric patients under 18 years of age have not been established.

11.5 Geriatric Use

Linagliptin is minimally excreted by the kidney; however, metformin is substantially excreted by the kidney *[see Warnings and Precautions (8.1) and Clinical Pharmacology (14.3)]*.

Linagliptin

In the 15 type 2 diabetes studies with linagliptin, 1085 linagliptin-treated patients were 65 years of age and older (including 131 linagliptin-treated patients 75 years of age and older). Of these 15 studies, 12 were double-blind placebo-controlled. In these 12 studies, 591 linagliptin-treated patients were 65 years of age and older (including 82 linagliptin-treated patients 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.

Metformin

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients.
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients *[see Contraindications (7), Warnings and Precautions (8.1), and Clinical Pharmacology (14.3)]*.

11.6 Renal Impairment

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. TRAJENTA DUO is contraindicated in severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2 *[see Dosage and Administration (5.2), Contraindications (7), Warnings and Precautions (8.1), and Clinical Pharmacology (14.3)]*.

If TRAJENTA DUO is discontinued due to evidence of renal impairment, linagliptin may be continued as a single entity tablet at the same total daily dose of 5 mg. No dose adjustment of linagliptin is recommended in patients with renal impairment.

In the linagliptin treatment arm of the CARMELINA trial *[see Clinical Studies (16.2)]*, 2200 (63%) patients had renal impairment (eGFR <60 mL/min/1.73m^2). 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 linagliptin and placebo treatment arms.

11.7 Hepatic Impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. TRAJENTA DUO is not recommended in patients with hepatic impairment *[see Warnings and Precautions (8.1)]*.

12 OVERDOSAGE

In the event of an overdose with TRAJENTA DUO contact your doctor immediately. Removal of linagliptin by hemodialysis or peritoneal dialysis is unlikely. However, metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful partly for removal of accumulated metformin from patients in whom TRAJENTA DUO overdosage is suspected.

Metformin
Overdose of metformin has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases *[see Boxed Warning and Warnings and Precautions (8.1)]*.

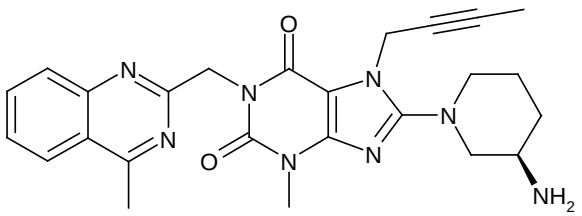
13 DESCRIPTION

TRAJENTA DUO tablets contain 2 oral antihyperglycemic drugs used in the management of type 2 diabetes mellitus: linagliptin and metformin hydrochloride.

Linagliptin
Linagliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme.

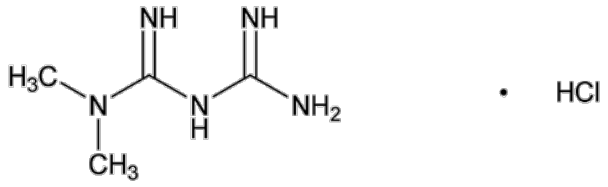
Linagliptin is described chemically as 1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl)methyl]-

The empirical formula is $C_{25}H_{28}N_8O_2$ 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).

Metformin Hydrochloride
Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.63 g/mol. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula is:



TRAJENTA DUO
TRAJENTA DUO is available for oral administration as tablets containing 2.5 mg linagliptin and 500 mg metformin hydrochloride (TRAJENTA DUO 2.5 mg/500 mg), 850 mg metformin hydrochloride (TRAJENTA DUO 2.5 mg/850 mg) or 1000 mg metformin hydrochloride (TRAJENTA DUO 2.5 mg/1000 mg). Each film-coated tablet of TRAJENTA DUO contains the following inactive ingredients: arginine, maize starch, copovidone, silica colloidal anhydrous, magnesium stearate, hypromellose, propylene glycol, titanium dioxide, , talc, yellow ferric oxide (2.5 mg/500 mg; 2.5 mg/850 mg) and/or red ferric oxide (2.5 mg/850 mg; 2.5 mg/1000 mg).

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

TRAJENTA DUO
TRAJENTA DUO combines 2 antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes mellitus: linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin, a member of the biguanide class.

Linagliptin
Linagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic 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.

Metformin

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

14.2 Pharmacodynamics

Linagliptin

Linagliptin binds to DPP-4 in a reversible manner and increases the concentrations of incretin hormones. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion, thus resulting in a better regulation of the 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.

14.3 Pharmacokinetics

TRAJENTA DUO

The results of a bioequivalence study in healthy subjects demonstrated that TRAJENTA DUO (linagliptin/metformin hydrochloride) 2.5 mg/500 mg, 2.5 mg/850 mg, and 2.5 mg/1000 mg combination tablets are bioequivalent to coadministration of corresponding doses of linagliptin and metformin as individual tablets. Administration of linagliptin 2.5 mg/metformin hydrochloride 1000 mg fixed-dose combination with food resulted in no change in overall exposure of linagliptin. There was no change in metformin 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.

Absorption

Linagliptin

The absolute bioavailability of linagliptin is approximately 30%. Following oral administration, 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. However, the prolonged elimination 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. 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.

Metformin
The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin tablets 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.

Distribution
Linagliptin
The mean apparent volume of distribution at steady state following a single intravenous dose of linagliptin 5 mg to healthy subjects is approximately 1110 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% to 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.

Metformin
The apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin hydrochloride tablets 850 mg averaged 654±358 L. Metformin is negligibly bound to plasma proteins, in contrast to SUs, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin tablets, steady-state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 mcg/mL. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Elimination
Linagliptin
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.

Metformin
Metformin has a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Metabolism
Linagliptin
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.

Metformin
Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

Excretion
Linagliptin
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.
Metformin
Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Specific Populations
Renal Impairment
TRAJENTA DUO: Studies characterizing the pharmacokinetics of linagliptin and metformin after administration of TRAJENTA DUO in renally impaired patients have not been performed*[see Contraindications (7) and Warnings and Precautions (8.1)].*

Linagliptin: 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 ($AUC_{\tau,ss}$ 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 AUC by 42% and C_{max} by 35%). For both type 2 diabetes mellitus groups, renal excretion was below 7% of the administered dose.

Metformin: In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased *[see Contraindications (7) and Warnings and Precautions (8.1)].*

Hepatic Impairment

TRAJENTA DUO: Studies characterizing the pharmacokinetics of linagliptin and metformin after administration of TRAJENTA DUO in hepatically impaired patients have not been performed *[see Warnings and Precautions (8.4)]*.

Linagliptin: In patients with mild hepatic impairment (Child-Pugh class A) steady-state exposure ($AUC_{\tau,ss}$) 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.

Metformin hydrochloride: No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

Body Mass Index (BMI)/Weight

Linagliptin: BMI/Weight had no clinically meaningful effect on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis.

Gender

Linagliptin: Gender had no clinically meaningful effect on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis.

Metformin hydrochloride: Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes mellitus when analyzed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes mellitus, the antihyperglycemic effect of metformin was comparable in males and females.

Geriatric

TRAJENTA DUO: Studies characterizing the pharmacokinetics of linagliptin and metformin after administration of TRAJENTA DUO in geriatric patients have not been performed. *[see Warnings and Precautions (8.1) and Use in Specific Populations (11.5)]*.

Linagliptin: Age did not have a clinically meaningful impact on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis.

Metformin hydrochloride: Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared with healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Pediatric

Studies characterizing the pharmacokinetics of linagliptin and metformin after administration of TRAJENTA DUO in pediatric patients have not yet been performed.

Race

Linagliptin: Race had no clinically meaningful effect on the pharmacokinetics of linagliptin based on available pharmacokinetic data, including subjects of White, Hispanic, Black, and Asian racial groups.

Metformin hydrochloride: No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes mellitus, the antihyperglycemic effect was comparable in Caucasians (n=249), Blacks (n=51), and Hispanics (n=24).

Drug Interactions

Pharmacokinetic drug interaction studies with TRAJENTA DUO have not been performed; however, such studies have been conducted with the individual components of TRAJENTA DUO (linagliptin and metformin hydrochloride).

Linagliptin

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 (10)]*.. *In vivo* studies indicated evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-gp, and OCT.

Table 2 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 (10.2)]*.
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 3 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}
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 metabolite M-III metabolite M-IV	0.94 0.98 1.04	0.86 0.96 1.05
Digoxin	0.25 mg QD	5 mg QD	digoxin	1.02	0.94
Simvastatin	40 mg QD	10 mg QD	simvastatin simvastatin acid	1.34 1.33	1.10 1.21
Warfarin	10 mg#	5 mg QD	R-warfarin S-warfarin INR PT	0.99 1.03 0.93** 1.03**	1.00 1.01 1.04** 1.15**
Ethinylestradiol and levonorgestrel	ethinylestradiol 0.03 mg and levonorgestrel 0.150 mg QD	5 mg QD	ethinylestradiol levonorgestrel	1.01 1.09	1.08 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

<u>Metformin hydrochloride</u>

Table 4 Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

Coadministered Drug	**Dosing of Coadministered Drug***	**Dosing of Metformin***	**Geometric Mean Ratio (ratio with/without coadministered drug) No effect=1.0**		
				AUC†	C_{max}
Glyburide	5 mg	850 mg	metformin	0.91‡	0.93‡
Furosemide	40 mg	850 mg	metformin	1.09‡	1.22‡
Nifedipine	10 mg	850 mg	metformin	1.16	1.21
Propranolol	40 mg	850 mg	metformin	0.90	0.94
Ibuprofen	400 mg	850 mg	metformin	1.05‡	1.07‡
Cationic drugs eliminated by renal tubular secretion may reduce metformin elimination *[see Drug Interactions (10.1)].*					
Cimetidine	400 mg	850 mg	metformin	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis *[see Drug Interactions (10.1)].*					
Topiramate**	100 mg	500 mg	metformin	1.25	1.17

* All metformin and coadministered drugs were given as single doses
† AUC = AUC(INF)
‡ Ratio of arithmetic means
**At steady state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours; AUC = AUC0-12h

Table 5 Effect of Metformin on Coadministered Drug Systemic Exposure

Coadministered Drug	**Dosing of Coadministered Drug***	**Dosing of Metformin***	**Geometric Mean Ratio (ratio with/without metformin) No effect=1.0**		
				AUC†	C_{max}
Glyburide	5 mg	850 mg§	glyburide	0.78‡	0.63‡
Furosemide	40 mg	850 mg	furosemide	0.87‡	0.69‡
Nifedipine	10 mg	850 mg	nifedipine	1.10§	1.08
Propranolol	40 mg	850 mg	propranolol	1.01§	1.020
Ibuprofen	400 mg	850 mg	ibuprofen	0.97¶	1.01¶
Cimetidine	400 mg	850 mg	cimetidine	0.95§	1.01

* All metformin and coadministered drugs were given as single doses
† AUC = AUC(INF) unless otherwise noted
‡ Ratio of arithmetic means, p-value of difference <0.05
§ AUC(0-24 hours) reported
¶ Ratio of arithmetic means

15 NONCLINICAL TOXICOLOGY

15.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

TRAJENTA DUO
No animal studies have been conducted with the combined products in TRAJENTA DUO to evaluate carcinogenesis, mutagenesis, or impairment of fertility. General toxicity studies in rats up to 13 weeks were performed with TRAJENTA DUO.

The following data are based on the findings in studies with linagliptin and metformin individually.

Linagliptin
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).

Metformin Hydrochloride
Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2000 mg/kg/day based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*Salmonella typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 2 times the MRHD based on body surface area comparisons.

16 CLINICAL STUDIES

The coadministration of linagliptin and metformin has been studied in patients with type 2 diabetes mellitus inadequately controlled on diet and exercise and in combination with sulfonylurea.

There have been no clinical efficacy studies conducted with TRAJENTA DUO; however, bioequivalence of TRAJENTA DUO to linagliptin and metformin coadministered as individual tablets was demonstrated in healthy subjects.

16.1 Glycemic Control Trials

Initial Combination Therapy with Linagliptin and Metformin

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 study designed to assess the efficacy of linagliptin 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 ≥7.0% to ≤10.5%) were randomized. Patients with inadequate glycemic control (A1C ≥7.5% to <11.0%) not on antihyperglycemic agents at study 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 ≥8.5%) and use of a prior oral antidiabetic drug (none vs monotherapy). Patients were randomized in a 1:2:2:2:2:2 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 linagliptin once daily, 500 mg or 1000 mg of metformin twice daily, or 2.5 mg of linagliptin twice daily in combination with 500 mg or 1000 mg of metformin twice daily. Patients who failed to meet specific glycemic goals during the study 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 6, Figure 1). 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 1000 mg twice daily compared to metformin 1000 mg twice daily; -1.1% (95% CI -1.4, -0.9; p<0.0001) for linagliptin 2.5 mg/metformin 1000 mg twice daily compared to linagliptin 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 linagliptin 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 6 Glycemic Parameters at Final Visit (24-Week Study) for Linagliptin and Metformin, Alone and in Combination in Randomized 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**
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)

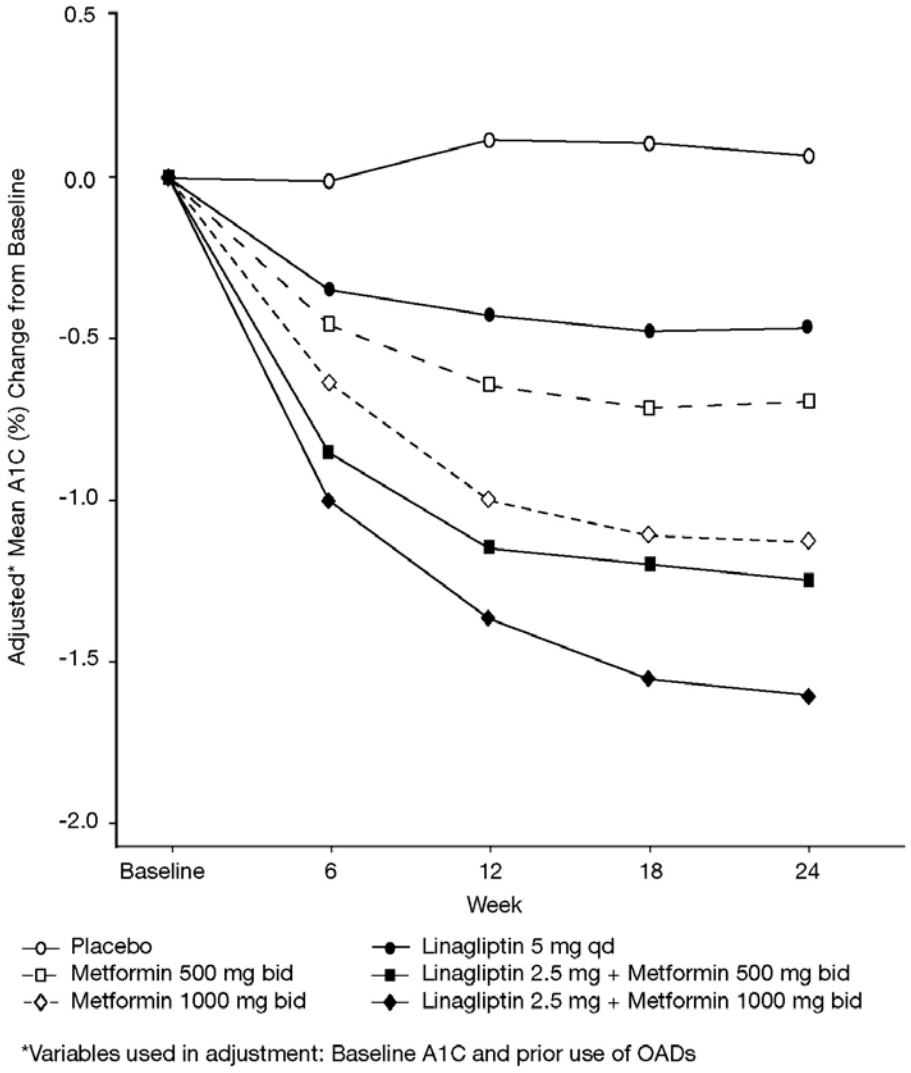
* Total daily dose of linagliptin is equal to 5 mg

** Full analysis population using last observation on study

*** Metformin 500 mg twice daily, n=140; Linagliptin 2.5 mg twice daily + Metformin 500 mg twice daily, n=136; Metformin 1000 mg twice daily, n=137; Linagliptin 2.5 mg twice daily + Metformin 1000 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.

Figure 1 Adjusted Mean Change from Baseline for A1C (%) over 24 Weeks with Linagliptin and Metformin, Alone and in Combination in Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Diet and Exercise - FAS completers.



*Variables used in adjustment: Baseline A1C and prior use of OADs

Initial Combination Therapy with Linagliptin and Metformin vs Linagliptin in Treatment-Naïve Patients

A total of 316 patients with type 2 diabetes diagnosed within the previous 12 months and treatment-naïve (no antidiabetic therapy for 12 weeks prior to randomization) and inadequate glycemic control (A1C ≥8.5% to ≤12.0%) participated in a 24-week, randomized, double-blind, study designed to assess the efficacy of linagliptin in combination with metformin vs linagliptin. Patients were randomized (1:1), after a 2-week run-in period, to either linagliptin 5 mg plus metformin (1500 to 2000 mg per day, n=159) or linagliptin 5 mg plus placebo, (n=157) administered once daily. Patients in the linagliptin and metformin treatment group were up-titrated to a maximum tolerated dose of metformin (1000 to 2000 mg per day) over a three-week period.

Initial therapy with the combination of linagliptin and metformin provided statistically significant improvements in A1C compared to linagliptin (Table 7). The mean difference between groups in A1C change from baseline was -0.8% with 2-sided 95% confidence interval (-1.23%, -0.45%).

Table 7 Glycemic Parameters at 24 Weeks in Study Comparing Linagliptin in Combination with Metformin to Linagliptin in Treatment-Naïve Patients*

	Linagliptin 5 mg + Metformin	**Linagliptin 5 mg + Placebo**
A1C (%) *		
Number of patients	n=153	n=150
Baseline (mean)	9.8	9.9
Change from baseline (adjusted mean)	-2.9	-2
Difference from linagliptin (adjusted mean**) (95% CI)	-0.84† (-1.23, -0.45)	--
Patients [n (%)] achieving A1C <7% *	82 (53.6)	45 (30)
FPG (mg/dL) *		
Number of patients	n=153	n=150
Baseline (mean)	196	198
Change from baseline (adjusted mean)	-54	-35
Difference from linagliptin (adjusted mean**) (95% CI)	-18†† (-31, -5.5)	--

†p<0.0001 compared to linagliptin, ††p=0.0054 compared to linagliptin
*Full analysis set population
**A1C: MMRM model included treatment, continuous baseline A1C, baseline A1C by visit interaction, visit by treatment interaction, baseline renal impairment by treatment interaction and baseline renal impairment by treatment by visit interaction. FPG: MMRM model included treatment, continuous baseline A1C, continuous baseline FPG, baseline FPG by visit interaction, visit by treatment interaction, baseline renal impairment by treatment interaction and baseline renal impairment by treatment by visit interaction.

The adjusted mean changes for A1C (%) from baseline over time for linagliptin and metformin as compared to linagliptin alone were maintained throughout the 24 week treatment period. Using the completers analysis the respective adjusted means for A1C (%) changes from baseline for linagliptin and metformin as compared to linagliptin alone were -1.9 and -1.3 at week 6, -2.6 and -1.8 at week 12, -2.7 and -1.9 at week 18, and -2.7 and -1.9 at week 24.

Changes in body weight from baseline were not clinically significant in either treatment group.

Add-On Combination Therapy With Metformin
A total of 701 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of linagliptin in combination with metformin. Patients already on metformin (n=491) at a dose of at least 1500 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 dose of at least 1500 mg per day) in monotherapy. Patients were randomized to the addition of either linagliptin 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, linagliptin provided statistically significant improvements in A1C, FPG, and 2-hour PPG compared with placebo (Table 8). Rescue glycemic therapy was used in 7.8% of patients treated with linagliptin 5 mg and in 18.9% of patients treated with placebo. A similar decrease in body weight was observed for both treatment groups.

Table 8 Glycemic Parameters in Placebo-Controlled Study for Linagliptin in Combination with Metformin*

	Linagliptin 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 study
** Linagliptin 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.

Active-Controlled Study vs Glimepiride in Combination With Metformin

The efficacy of linagliptin was evaluated in a 104-week double-blind, glimepiride-controlled non-inferiority study in type 2 diabetic patients 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 (dose of ≥1500 mg per 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 linagliptin 5 mg once daily or glimepiride. Randomization was stratified by baseline HbA1c (<8.5% vs ≥8.5%), and the previous use of antidiabetic drugs (metformin alone vs metformin plus one other OAD). Patients receiving glimepiride were given an initial dose of 1 mg/day and then electively titrated over the next 12 weeks to a maximum dose of 4 mg/day as needed to optimize glycemic control. Thereafter, the glimepiride dose was to be kept constant, except for down-titration to prevent hypoglycemia.

After 52 weeks and 104 weeks, linagliptin and glimepiride both had reductions from baseline in A1C (52 weeks: -0.4% for linagliptin, -0.6% for glimepiride; 104 weeks: -0.2% for linagliptin, -0.4% for glimepiride) from a baseline mean of 7.7% (Table 9). 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 9 Glycemic Parameters at 52 and 104 Weeks in Study Comparing Linagliptin to Glimepiride as Add-On Therapy in Patients Inadequately Controlled on Metformin**

	Week 52		Week 104	
	Linagliptin 5 mg + Metformin	**Glimepiride + Metformin (mean glimepiride dose 3 mg)**	**Linagliptin 5 mg + Metformin**	**Glimepiride + Metformin (mean glimepiride dose 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

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

** Full analysis population using last observation on study

**** 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. 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 Metformin and a Sulfonylurea

A total of 1058 patients with type 2 diabetes mellitus participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of linagliptin in combination with a sulfonylurea and metformin. The most common sulfonylureas used by patients in the study were glimepiride (31%), glibenclamide (26%), and gliclazide (26% [not available in the United States]). Patients on a sulfonylurea and metformin were randomized to receive linagliptin 5 mg or placebo, each administered once daily. Patients who failed to meet specific glycemic goals during the study were treated with pioglitazone rescue. Glycemic end points measured included A1C and FPG.

In combination with a sulfonylurea and metformin, linagliptin provided statistically significant improvements in A1C and FPG compared with placebo (Table 10). In the entire study population

(patients on linagliptin in combination with a 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 linagliptin 5 mg and in 13% of patients treated with placebo. Change from baseline in body weight did not differ significantly between the groups.

Table 10 Glycemic Parameters at Final Visit (24-Week Study) for Linagliptin in Combination With Metformin and Sulfonylurea*

	Linagliptin 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 study
** Linagliptin 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.

16.2 Linagliptin Cardiovascular Safety Trial

CARMELINA

The cardiovascular risk of linagliptin was evaluated in CARMELINA, a multi-national, multi-center, placebo-controlled, double-blind, parallel group trial comparing linagliptin (N=3494) to placebo (N=3485) 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 linagliptin and placebo when these were added to standard of care treatments for diabetes 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, 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% Caucasian, 9% Asian, and 6% Black. 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, nonfatal myocardial infarction or nonfatal stroke. The study 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 11. The estimated hazard ratio for MACE associated with linagliptin 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 2.

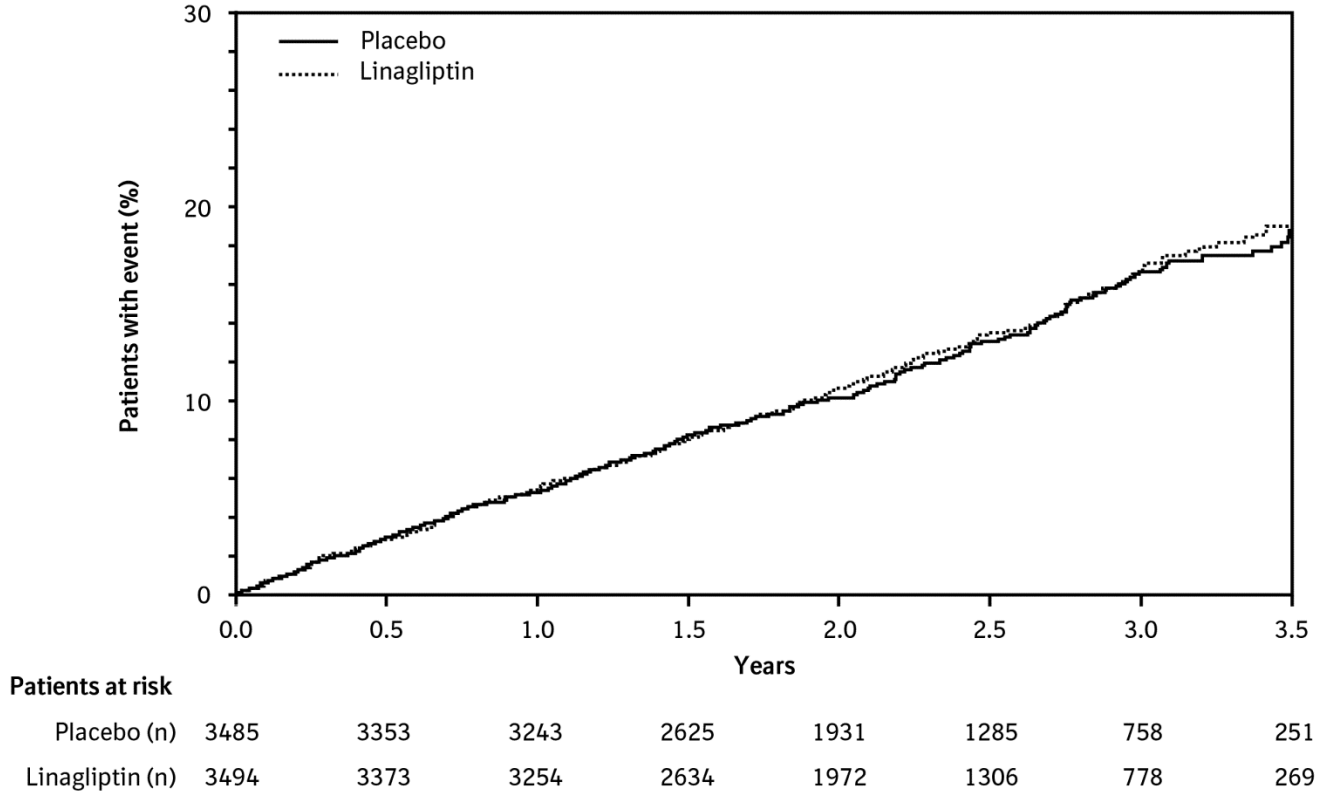
Table 11 Major Adverse Cardiovascular Events (MACE) by Treatment Group in the CARMELINA Trial

	Linagliptin 5 mg n = 3494		**Placebo n = 3485**		**Hazard Ratio**
	Number of Subjects (%)	**Incidence Rate per 1000 PY***	**Number of Subjects (%)**	**Incidence Rate per 1000 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)
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 2 Kaplan-Meier: Time to First Occurrence of MACE in the CARMELINA Trial



CAROLINA
The cardiovascular risk of linagliptin was evaluated in CAROLINA, a multi-center, multi-national, randomized, double-blind, parallel group trial comparing linagliptin (N=3023) to glimepiride (N=3010) 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 linagliptin and glimepiride when these were added to standard of care treatments for diabetes 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 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 >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% Caucasian, 18% Asian, and 5% Black. The mean HbA1c was 7.15% and mean duration of type 2 diabetes 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 m^2. The mean eGFR was 77 mL/min/1.73 m^2. 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 study 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 12. The Kaplan-Meier curve depicting time to first occurrence of MACE is shown in Figure 3.

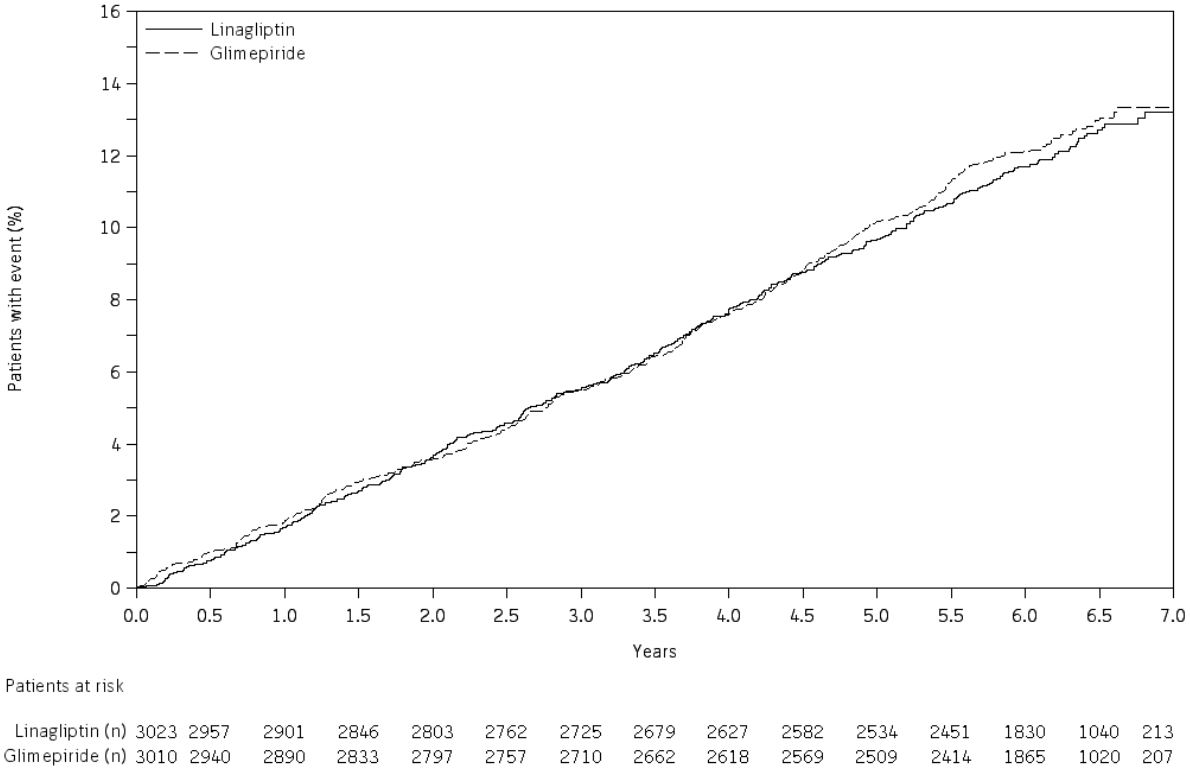
Table 12 Major Adverse Cardiovascular Events (MACE) by Treatment Group in the CAROLINA Study

	Linagliptin 5 mg n=3023		**Glimepiride (1 mg to 4 mg) n=3010**		**Hazard Ratio**
	Number of Subjects (%)	**Incidence Rate per 1000 PY***	**Number of Subjects (%)**	**Incidence Rate per 1000 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 3 Time to First Occurrence of 3P-MACE in CAROLINA



17 HOW SUPPLIED/STORAGE AND HANDLING

Blister packs are available with 14 and 60 film-coated tablets.
Not all the pack sizes may be marketed.
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19 REGISTRATION HOLDER / NUMBER

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