PRODUCT MONOGRAPH

Pr JENTADUETO®

linagliptin and metformin hydrochloride tablets

2.5 mg/500 mg, 2.5 mg/850 mg and 2.5 mg/1000 mg linagliptin/metformin hydrochloride, tablets, oral

ATC Code: A10BD11

Combinations of oral blood glucose lowering drugs

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Oral	Tablets: 2.5 mg/500 mg 2.5 mg/850 mg 2.5 mg/1000 mg	*For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

INDICATIONS AND CLINICAL USE

JENTADUETO (linagliptin/metformin hydrochloride tablets) is indicated as an adjunct to diet and exercise, to improve glycemic control in adult patients with type 2 diabetes mellitus who are:

- inadequately controlled on metformin, or
- already controlled with the free combination of linagliptin and metformin.

JENTADUETO (linagliptin/metformin hydrochloride tablets) is indicated as an adjunct to diet and exercise, to improve glycemic control in adult patients with type 2 diabetes mellitus:

- in combination with a sulfonylurea, when dual therapy with metformin and a sulfonylurea do not provide adequate glycemic control, or
- in combination with basal insulin, when dual therapy with metformin and basal insulin do not provide adequate glycemic control.

See CLINICAL TRIALS section.

Geriatrics (≥65 years of age): JENTADUETO should be used with caution in geriatric patients. As metformin is excreted via the kidney and aging can be associated with reduced renal function, care should be taken in dose selection in patients with advanced age. More careful and frequent monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly patients (see WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

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

CONTRAINDICATIONS

- Unstable and/or insulin-dependent (type 1) diabetes mellitus.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma, history of ketoacidosis with or without coma.
- In patients with a history of lactic acidosis, irrespective of precipitating factors (see WARNINGS AND PRECAUTIONS).
- In the presence of severe renal impairment [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2], end-stage renal disease, in patients on dialysis or when renal function is not known (see WARNINGS AND PRECAUTIONS).
- In excessive alcohol intake, acute or chronic.
- In patients suffering from severe hepatic dysfunction, since severe hepatic dysfunction has been associated with some cases of lactic acidosis. JENTADUETO should not be used in patients with clinical or laboratory evidence of hepatic disease.
- In cases of cardiovascular collapse and in disease states associated with hypoxemia such as cardiorespiratory insufficiency, which are often associated with hyperlactacidemia.
- During stress conditions, such as severe infections, trauma or surgery and the recovery phase thereafter.
- In patients suffering from severe dehydration or shock.
- Known hypersensitivity to linagliptin, metformin or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS). For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section.
- During pregnancy and breastfeeding (see WARNINGS AND PRECAUTIONS).
- During period around administration of iodinated contrast materials, because the use of such products may result in acute alteration of renal function (see WARNINGS AND PRECAUTIONS).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Lactic Acidosis

- Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with JENTADUETO. The risk increases with conditions such as renal impairment, sepsis, dehydration, excess alcohol intake, hepatic impairment, and acute congestive heart failure (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism – Lactic Acidosis).

- Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking JENTADUETO, since alcohol intake potentiates the effect of metformin on lactate metabolism (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism – Lactic Acidosis).

General

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

Cardiovascular

Heart Failure:

Linagliptin

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

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

Hypoxic States:

Metformin hydrochloride

Cardiovascular collapse (shock) from whatever cause (e.g., acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia) have been associated with lactic acidosis and may also cause prerenal azotemia (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism). When such events occur in patients on JENTADUETO therapy, the drug should be promptly discontinued.

Endocrine and Metabolism

Hypoglycemia:

Linagliptin

Caution is advised when JENTADUETO is used in combination with a sulfonylurea or insulin. When linagliptin and metformin were used in combination with a sulfonylurea, the incidence of hypoglycemia was increased over the placebo in combination with a sulfonylurea plus metformin (see ADVERSE REACTIONS). Sulfonylureas and insulin are known to cause hypoglycemia. Therefore, to reduce the risk of hypoglycemia associated with these indications, a lower dose of sulfonylurea or insulin may be considered (see DOSAGE AND ADMINISTRATION).

Metformin hydrochloride
Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but 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 sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking β-adrenergic blocking drugs.

Hypothyroidism:
Metformin hydrochloride
Metformin induces a reduction in thyrotropin (thyroid stimulating hormone (TSH)) levels in patients with treated or untreated hypothyroidism (see ADVERSE REACTIONS). Regular monitoring of TSH levels is recommended in patients with hypothyroidism (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Studies have shown that metformin reduces plasma TSH levels, often to subnormal levels, when it is administered to patients with untreated hypothyroidism or to hypothyroid patients effectively treated with levothyroxine. The metformin-induced reduction of plasma TSH levels is not observed when metformin is administered to patients with normal thyroid function. Metformin has been suggested to enhance the inhibitory modulation of thyroid hormones on TSH secretion**.**

Levothyroxine can reduce the hypoglycemic effect of metformin. Careful monitoring of blood glucose levels is recommended in patients with hypothyroidism treated with levothyroxine, especially when thyroid hormone therapy is initiated, changed, or stopped (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and DRUG INTERACTIONS).

Lactic Acidosis:
Metformin hydrochloride
Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with JENTADUETO; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications (see DOSAGE AND ADMINISTRATION).

Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age (see WARNINGS AND PRECAUTIONS, Special Populations). The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin.

In addition, JENTADUETO should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking JENTADUETO, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, JENTADUETO should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure.

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur. JENTADUETO should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling.

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking JENTADUETO, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Cardiovascular, Hepatic and Renal).

Physicians should instruct their patients to recognize the symptoms which could be a signal of the onset of lactic acidosis. If acidosis of any kind develops, JENTADUETO should be discontinued immediately and the patient should be immediately hospitalized.

Change in Clinical Status of Previously Controlled Diabetes Patients:
Metformin hydrochloride
A diabetic patient previously well controlled on JENTADUETO 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, JENTADUETO must be stopped immediately and appropriate corrective measures initiated.

Loss of Control of Blood Glucose: The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy. Should secondary failure occur with JENTADUETO, therapeutic alternatives should be considered.

Metformin hydrochloride
When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold JENTADUETO and temporarily administer insulin. JENTADUETO may be reinstituted after the acute episode is resolved.

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

Vitamin B_{12} Levels:
Metformin hydrochloride
Impairment of vitamin B_{12} absorption has been reported in some patients treated with metformin. Therefore, measurements of serum vitamin B_{12} are advisable at least every one to two years in patients on long-term treatment with JENTADUETO.

A decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, is observed in approximately 7% of patients receiving metformin in controlled clinical trials of 29 weeks duration. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on JENTADUETO and any apparent abnormalities should be appropriately investigated and managed (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests). Certain individuals (those with inadequate Vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B_{12} levels.

Long-term treatment with metformin has been associated with a decrease in serum vitamin B_{12} levels which may cause peripheral neuropathy. Serious cases of peripheral neuropathy have been reported with metformin treatment, one of the components of JENTADUETO, in the context of vitamin B_{12} deficiency (see ADVERSE REACTIONS). Monitoring of serum vitamin B_{12} levels is recommended (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Hematologic
Metformin hydrochloride
Serious cases of metformin-induced hemolytic anemia, some with a fatal outcome, have been reported (see ADVERSE REACTIONS). Two mechanisms were described for the metformin-induced immune hemolytic anemia; formation of an antibody against the erythrocyte-metformin complex and autoantibody formation. Monitoring of hematologic parameters is recommended (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Hepatic/Biliary/Pancreatic
Hepatic: JENTADUETO is contraindicated in patients with severe hepatic dysfunction and should not be used in patients with clinical or laboratory evidence of hepatic disease (see CONTRAINDICATIONS).

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

Metformin hydrochloride
Impaired hepatic function has been associated with some cases of lactic acidosis.

Pancreatitis:
Linagliptin

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

Metformin hydrochloride
Serious cases of pancreatitis have been reported in patients receiving metformin (see ADVERSE REACTIONS). The reported pancreatitis cases occurred either in the context of an acute metformin overdose (see OVERDOSAGE) or in patients receiving therapeutic doses of metformin with concurrent renal failure and/or lactic acidosis, indicating metformin accumulation.

Immune

Hypersensitivity Reactions:

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

Immunocompromised Patients:

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

Monitoring and Laboratory Tests

Periodic cardiovascular, ophthalmic, hematological, hepatic, and renal assessments are recommended (see WARNINGS AND PRECAUTIONS).

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

More frequent glucose monitoring should be considered when JENTADUETO is simultaneously administered with cationic drugs that are excreted via renal tubular secretion, or with drugs that produce hyperglycemia or hypoglycemia, especially at the initiation of treatment with the interfering drug(s) (see DRUG INTERACTIONS).

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

Hematology: Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with metformin therapy, if this is suspected, vitamin B_{12} deficiency should be excluded. Periodic measurements of serum vitamin B_{12} levels should be performed in patients on long-term treatment with JENTADUETO, especially in patients with anemia or neuropathy (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

A close monitoring of the International Normalized Ratio (INR) is recommended in patients concurrently administering metformin and phenprocoumon or other antivitamin K anticoagulants (see DRUG INTERACTIONS).

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

Hypothyroidism: Regular monitoring of thyroid-stimulating hormone (TSH) levels is recommended in patients with hypothyroidism.

For hypothyroid patients treated with levothyroxine, careful monitoring of blood glucose levels is recommended, especially when thyroid hormone therapy is initiated, changed, or stopped (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism and DRUG INTERACTIONS).

For patients concurrently administering metformin and phenprocoumon or other antivitamin K anticoagulants, a close monitoring of the International Normalized Ratio (INR) is recommended (see DRUG INTERACTIONS).

Renal Function: JENTADUETO is contraindicated in patients with an estimated glomerular rate (eGFR) <30 mL/min/1.73 m^2 (see CONTRAINDICATIONS). Renal function must be assessed prior to initiation of JENTADUETO and periodically thereafter; at least once a year in patients with normal renal function, and more frequent monitoring in patients with renal

impairment (eGFR <60 mL/min/1.73 m^2) and in elderly patients (see DOSAGE AND ADMINISTRATION).

Monitoring of renal function is recommended prior to and following initiation of any concomitant drug which might have an impact on renal function (see DRUG INTERACTIONS).

Neurologic

Metformin hydrochloride

Serious cases of metformin-induced encephalopathy have been reported (see ADVERSE REACTIONS). Some of these cases were reported without association with lactic acidosis, hypoglycemia, or renal impairment.

Peri-Operative Consideration

Metformin hydrochloride

JENTADUETO therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids). JENTADUETO should be discontinued 2 days before surgical intervention and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as acceptable and found to be stable (see DOSAGE AND ADMINISTRATION).

Renal

JENTADUETO is contraindicated in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) (see CONTRAINDICATIONS).

Before initiation of JENTADUETO therapy and regularly thereafter, renal function must be assessed. In patients with eGFR less than 60 mL/min/1.73 m^2, more intensive monitoring for glycemic and renal biomarkers and signs and symptoms of renal dysfunction is recommended, especially if the eGFR is less than 45 mL/min/1.73 m^2 (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and DOSAGE AND ADMINISTRATION).

In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and JENTADUETO discontinued if evidence of renal impairment is present.

Special caution should be exercised in situations where renal function may become impaired, for example in the elderly, in the case of dehydration when initiating antihypertensive therapy or diuretic therapy or when starting therapy with a non-steroidal anti-inflammatory drug (NSAID). Therefore, consider more frequent monitoring of patients.

Linagliptin

Clinical study experience with linagliptin in patients with end-stage renal disease (ESRD) and those on dialysis is limited.

Metformin hydrochloride
Metformin is known to be substantially excreted by the kidney and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function.

In patients with advanced age, JENTADUETO should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, renal function should be monitored regularly. Decreased renal function in elderly subjects is frequent and asymptomatic.

Use of concomitant medications that may affect renal function or metformin disposition: Concomitant medication(s), that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see DRUG INTERACTIONS), should be used with caution. The concomitant use of JENTADUETO with these specific drugs may increase the risk of metformin-associated lactic acidosis and therefore, consider more frequent monitoring of patients.

Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials): Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see CONTRAINDICATIONS). Therefore, in patients with a history of hepatic impairment, alcoholism, or heart failure, or in patients who will be administered intra-arterial iodinated contrast, JENTADUETO should be 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 re-evaluated and found to be acceptable and stable (see DOSAGE AND ADMINISTRATION).

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

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

Bullous Pemphigoid: Cases of bullous pemphigoid have been reported with the use of linagliptin. In a long-term cardiovascular outcome trial, there have been reports of bullous pemphigoid in 7 (0.2%) in patients treated with linagliptin compared to none in patients treated

with placebo, and 3 of these patients were hospitalized due to bullous pemphigoid (see ADVERSE REACTIONS). Post-marketing cases of bullous pemphigoid requiring hospitalization have been reported with the use of DPP-4 inhibitors including linagliptin. 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 JENTADUETO. If bullous pemphigoid is suspected, JENTADUETO should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Special Populations

Pregnant Women: JENTADUETO is contraindicated for use in pregnancy (see CONTRAINDICATIONS). There are no adequate and well-controlled studies in pregnant women with JENTADUETO or its individual components; therefore the safety of JENTADUETO in pregnant women is not known. As animal reproductive studies are not always predictive of human response, JENTADUETO is contraindicated during pregnancy.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, insulin should be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Linagliptin

There are no adequate and well controlled studies of linagliptin in pregnant women; therefore the safety of linagliptin in pregnant women is not known.

Metformin hydrochloride

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, or about two and six times the maximum recommended human daily dose on a body surface area basis. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Nursing Women: JENTADUETO is contraindicated during breast-feeding (see CONTRAINDICATIONS). 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 hydrochloride is also excreted into human breast milk in very small amounts but it is not known whether linagliptin is secreted in human milk. Therefore, JENTADUETO should not be used by a woman during breastfeeding.

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

Geriatrics (≥65 years of age): Because metformin is substantially excreted by the kidney and because aging can be associated with reduced renal function, JENTADUETO should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function (see WARNINGS AND PRECAUTIONS,

Renal, and DOSAGE AND ADMINISTRATION).

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

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

Metformin hydrochloride
Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients. 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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
The safety of linagliptin 2.5 mg twice daily (or its bioequivalent of 5 mg once daily) plus metformin has been evaluated in over 3500 patients with type 2 diabetes mellitus.

In placebo-controlled studies of 12 to 24 weeks duration, more than 1300 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.

The placebo-controlled studies included 4 studies where linagliptin was given as add-on to metformin and 1 study where linagliptin was given as add-on to metformin + sulfonylurea.
In placebo-controlled studies the most frequently reported related adverse reaction for linagliptin + metformin was diarrhea (0.9%) with comparably low rate on metformin + placebo (1.2%).

Adverse reactions reported when linagliptin and metformin were combined with SU: When linagliptin and metformin were administered in combination with a sulfonylurea, hypoglycemia was the most commonly reported adverse event (linagliptin plus metformin plus sulfonylurea 22.9% vs. 14.8% in the placebo group) and identified as an additional adverse reaction under these conditions. None of the hypoglycemia episodes were classified as severe (requiring assistance).

Linagliptin
Linagliptin was generally well tolerated in controlled clinical studies with an overall incidence of

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

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

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

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

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

Metformin hydrochloride
The adverse events most commonly associated with metformin (linagliptin/metformin) are diarrhea, nausea, and upset stomach. Lactic acidosis is a rare, but serious side effect. Lactic acidosis is fatal in approximately 50% of cases.

Lactic Acidosis: very rare (<1/10, 000 and isolated reports) (see WARNINGS AND PRECAUTIONS, and OVERDOSAGE).

Gastrointestinal Reactions: very common (>1/10): Gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorexia) are the most common reactions to metformin and are approximately 30% more frequent in patients on metformin monotherapy than in placebo-treated patients, particularly during initiation of metformin therapy. These symptoms are generally transient and resolve spontaneously during continued treatment. Occasionally, temporary dose reduction may be useful.

Because gastrointestinal symptoms during therapy initiation appear to be dose-related, they may be decreased by gradual dose escalation and by having patients take metformin (metformin hydrochloride) with meals (see DOSAGE AND ADMINISTRATION).

Because significant diarrhea and/or vomiting can cause dehydration and prerenal azotemia, metformin should be temporarily discontinued, under such circumstances.

For patients who have been stabilized on metformin, non-specific gastrointestinal symptoms should not be attributed to therapy unless intercurrent illness or lactic acidosis have been excluded.

Special Senses: common (≥1/100): During initiation of metformin therapy complaints of taste disturbance are common, i.e. metallic taste.

Dermatologic Reactions: very rare (<1/10,000 and isolated reports): The incidence of rash/dermatitis in controlled clinical trials was comparable to placebo for metformin monotherapy and to sulfonylurea for metformin /sulfonylurea therapy. Reports of skin reactions such as erythema, pruritus, and urticaria are very rare.

Hematologic: Decrease of vitamin B_{12} absorption with decrease of serum levels during long-term use of metformin is rare (≥1/10,000 and <1/1,000). Consideration of such aetiology is recommended if a patient presents with megaloblastic anemia.

Hepatic: very rare (<1/10,000 and isolated reports): Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation has been documented in isolated reports.

Clinical Trial Adverse Drug Reactions

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

In a 24-week factorial design study (BI Study 1218.46) to compare free combination of linagliptin and metformin therapy versus respective monotherapies, adverse events reported regardless of causality in ≥2% of patients treated with linagliptin + metformin (regardless of metformin dose) and more commonly than in patients given placebo are shown in Table 1.

Table 1 Adverse Events Reported in ≥2% of Patients Treated with Linagliptin + Metformin and Greater than with Placebo (BI Study 1218.46), Irrespective of Causality by System Organ Class and Preferred Term

System Organ Class/ Preferred term	**Placebo N (%)**	**Linagliptin Monotherapy N (%)**	**Metformin Monotherapy N (%)**	**Combination of Linagliptin with Metformin N (%)**
Number of Patients	72 (100.0)	142 (100.0)	291 (100.0)	286 (100.0)
Gastrointestinal disorders	10 (13.9)	17 (12.0)	37 (12.7)	48 (16.8)
Diarrhea	2 (2.8)	5 (3.5)	11 (3.8)	18 (6.3)
Nausea	0 (0.0)	1 (0.7)	5 (1.7)	7 (2.4)
Infections and infestations	16 (22.2)	26 (18.3)	53 (18.2)	64 (22.4)
Nasopharyngitis	1 (1.4)	8 (5.6)	8 (2.7)	18 (6.3)
Upper respiratory tract infections	2 (2.8)	1 (0.7)	6 (2.1)	9 (3.1)
Urinary tract infection	2 (2.8)	2 (1.4)	7 (2.4)	9 (3.1)
Musculoskeletal and connective tissue disorders	5 (6.9)	13 (9.2)	21 (7.2)	27 (9.4)
Back pain	2 (2.8)	5 (3.5)	5 (1.7)	10 (3.5)
Nervous system disorders	3 (4.2)	11 (7.7)	25 (8.6)	27 (9.4)
Headache	1 (1.4)	6 (4.2)	10 (3.4)	8 (2.8)
Paraesthesia	1 (1.4)	1 (0.7)	4 (1.4)	6 (2.1)

In the pooled analysis of the 4 placebo-controlled trials, investigating the concomitant administration of linagliptin and metformin (1218.6, 1218.17, 1218.46, 1218.62), where 1322 patients received linagliptin and metformin and 583 patients received placebo plus metformin, the overall incidence of adverse events (AEs) in patients treated with placebo and metformin was comparable to linagliptin in combination with metformin (50.6% and 47.8% respectively). Discontinuation of therapy due to AEs was comparable in patients who received placebo and metformin to patients treated with linagliptin and metformin (2.6% and 2.3% respectively).

The incidence of AEs, reported regardless of causality assessment, in ≥2% of patients and occurring more frequently in patients treated with linagliptin 5 mg over placebo, as add-on to metformin, as add-on to metformin plus sulfonylurea are shown in Table 2 to Table 5.

Combination therapy: linagliptin add-on to metformin

Table 2 Linagliptin in Combination with Metformin (BI Study 1218.17, randomized, double-blind, placebo-controlled, parallel-group efficacy and safety study of linagliptin over 24 weeks in T2DM patients): Frequency of Adverse Events ≥2% and for Linagliptin in Excess over Placebo, Irrespective of Causality by System Organ Class and Preferred Term

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

Combination therapy: linagliptin add-on to metformin and a sulfonylurea

Table 3 Linagliptin in Combination with Metformin and Sulfonylurea (BI Study 1218.18, randomized, double-blind, placebo-controlled, parallel-group efficacy and safety study of linagliptin over 24 weeks in T2DM patients): Frequency of Adverse events ≥2% and for Linagliptin in Excess over Placebo, Irrespective of Causality by System Organ Class and Preferred Term

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

Combination therapy: linagliptin add-on to metformin versus sulfonylurea and metformin

Table 4 Linagliptin in Combination with Metformin (BI study 1218.20, randomized, double-blind, active-controlled, parallel-group efficacy and safety study of linagliptin as add-on combination use with metformin compared to a sulfonylurea agent (glimepiride) over 2 years in T2DM patients): Frequency of Adverse Events ≥2% and for Linagliptin in Excess over Placebo, Irrespective of Causality by System Organ Class and Preferred Term

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

Table 5 Linagliptin in Combination with Basal Insulin (pivotal trial, randomized, double-blind, placebo-controlled, parallel-group efficacy and safety study of linagliptin over 52 weeks in T2DM patients): Frequency of Adverse Events ≥2% and for Linagliptin in Excess over Placebo, Irrespective of Causality by System Organ Class and Preferred Term

System Organ Class/ Preferred term	**Placebo N (%)**	**Linagliptin N (%)**
Number of patients	630	631
General disorders and administration site conditions	74 (11.7)	84 (13.3)
Oedema peripheral	15 (2.4)	20 (3.2)
Fatigue	11 (1.7)	16 (2.5)
Infections and infestations	248 (39.4)	239 (37.9)
Nasopharyngitis	62 (9.8)	71 (11.3)
Upper respiratory tract infection	30 (4.8)	31 (4.9)
Sinusitis	10 (1.6)	17 (2.7)
Pharyngitis	9 (1.4)	14 (2.2)
Blood and lymphatic system disorders	20 (3.2)	26 (4.1)
Anaemia	12 (1.9)	20 (3.2)
Nervous System disorders	112 (17.8)	106 (16.8)
Headache	27 (4.3)	35 (5.5)
Dizziness	30 (4.8)	34 (5.4)
Eye disorders	50 (7.9)	57 (9.0)
Cataract	13 (2.1)	14 (2.2)
Diabetic retinopathy	7 (1.1)	13 (2.1)
Gastrointestinal disorders	126 (20.0)	140 (22.2)
Diarrhoea	30 (4.8)	33 (5.2)
Nausea	14 (2.2)	27 (4.3)
Constipation	9 (1.4)	15 (2.4)
Toothache	12 (1.9)	14 (2.2)
Musculoskeletal and connective tissue disorders	141 (22.4)	128 (20.3)
Back pain	30 (4.8)	35 (5.5)
Pain in extremity	20 (3.2)	24 (3.8)
Osteoarthritis	14 (2.2)	15 (2.4)
Investigations	62 (9.8)	65 (10.3)
Glycosylated hemoglobin increased	13 (2.1)	15 (2.4)
Injury, poisoning and procedural complications	77 (12.2)	77 (12.2)
Fall	13 (2.1)	16 (2.5)

Less Common Clinical Trial Adverse Drug Reactions ≥0.1% and <2% (Drug-Related and Greater than Placebo)

Blood and Lymphatic System Disorders: leukocytosis
Cardiac Disorders: acute myocardial infarction
Ear and Labyrinth Disorders: vertigo
Eye Disorders: conjunctivitis allergic
Gastrointestinal Disorders: abdominal discomfort, abdominal distension, abdominal pain upper, constipation, dyspepsia, gastritis, gastrointestinal disorder, gastrooesophageal reflux disease, irritable bowel syndrome, mouth ulceration, vomiting*
General Disorders and Administration Site Conditions: drug ineffective, gait disturbance
Hepatobiliary Disorders: hepatic steatosis
Infections and Infestations: nasopharyngitis*
Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, blood amylase increased, gamma-glutamyltransferase increased, hepatic enzyme increased, platelet count decreased, transaminases increased
Metabolism and Nutrition Disorders: decreased appetite*, dyslipidemia
Musculoskeletal and Connective Tissue Disorders: bursitis, muscle spasms, myalgia
Nervous System Disorders: aphasia, coordination abnormal, dizziness, headache, lethargy, tremor
Psychiatric Disorders: libido decreased
Respiratory and Thoracic: bronchial hyper-reactivity, rhinitis allergic, rhinorrhea, sneezing
Skin and Subcutaneous Tissue Disorders: alopecia, hyperhidrosis, pruritus*, rash
*BI assessed ADRs

Adverse Reactions in Specific Populations
Linagliptin Cardiovascular and Renal Safety Study (CARMELINA): For details pertaining to study design and patient populations, see CLINICAL TRIALS.

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

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

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

Hypoglycemia: A numerically higher rate of hypoglycemia was observed with linagliptin compared with placebo in patients taking sulfonylurea at baseline. Among patients who were using sulfonylurea at baseline, the incidence of severe hypoglycemia was 2.0% in linagliptin-treated patients and 1.7% in placebo-treated patients. Among patients who were using insulin at baseline, the incidence of severe hypoglycemia was 4.4% in linagliptin-treated patients and 4.9% in placebo-treated patients.

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

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

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

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

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

Abnormal Hematologic and Clinical Chemistry Findings

Linagliptin

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

- *Lipase:* Increases in blood lipase levels (in a 24-week clinical trial, 2.3% in placebo group and 9.9% in the linagliptin group experienced lipase levels >3 times upper limit of normal (ULN), during treatment or post-treatment period (approximately 4 weeks); the ULN for lipase level in blood was 60 U/L);
- *Hemoglobin:* Decreases in hemoglobin (4.0% in the placebo group, 7.4% in the linagliptin group; based on pooled placebo-controlled trials with insulin +/- antihyperglycemic agents background);
- *Amylase:* Increases in amylase (3.3% in the placebo group, 5.9% in the linagliptin group; based on pooled placebo-controlled trials with insulin +/- antihyperglycemic agents background). In an active-controlled cardiovascular safety study with linagliptin, 0.6% in the active-control (glimepiride) group and 1.0% in linagliptin group experienced amylase levels above 3 times ULN.

Metformin hydrochloride

During controlled clinical trials of 29 weeks duration, approximately 9% of patients on metformin monotherapy and 6% of patients on metformin /sulfonylurea therapy developed asymptomatic subnormal serum vitamin B_{12} levels; serum folic acid levels did not decrease significantly. Five cases of megaloblastic anemia have been reported with metformin administration and no increased incidence of neuropathy has been observed in clinical trials. However, serious cases of peripheral neuropathy have been reported with metformin treatment in the post-marketing experience in patients with vitamin B_{12} deficiency (see WARNINGS AND PRECAUTIONS).

Post-Marketing Adverse Drug Reactions

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.

Blood and Lymphatic System Disorders: hemolytic anemia, some with a fatal outcome (see WARNINGS AND PRECAUTIONS)

Gastrointestinal Disorders: abdominal discomfort, abdominal distension, abdominal pain, abdominal pain upper, acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis (see WARNINGS AND PRECAUTIONS), constipation, diarrhea, dry mouth, dyspepsia, flatulence, gastric disorder, gastric ulcer, gastrointestinal disorder, nausea, vomiting

Hepatobiliary Disorders: liver function tests abnormalities or hepatitis resolving upon metformin discontinuation, autoimmune hepatitis, drug-induced liver injury, hepatitis (see WARNINGS AND PRECAUTIONS)

Immune System Disorders: hypersensitivity reactions including anaphylaxis, angioedema, urticaria, rash, and exfoliative skin conditions (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS), mouth ulceration

Investigations: blood lactic acid increased, reduction of thyrotropin level in patients with treated or untreated hypothyroidism (see WARNINGS AND PRECAUTIONS)
Metabolism and Nutrition Disorders: lactic acidosis, decrease of vitamin B_{12} absorption with decrease of serum levels during long-term use of metformin, weight decreased, decreased appetite, peripheral neuropathy in patients with vitamin B_{12} deficiency, hypomagnesemia in the context of diarrhea (see WARNINGS AND PRECAUTIONS)
Musculoskeletal and Connective Tissue Disorders: arthralgia, rhabdomyolysis
Nervous System Disorders: encephalopathy (see WARNINGS AND PRECAUTIONS)
Skin and Subcutaneous Tissue Disorders: photosensitivity, erythema, pruritus, rash, skin lesion, urticaria, bullous pemphigoid (see WARNINGS AND PRECAUTIONS)

DRUG INTERACTIONS

Overview

Pharmacokinetic drug interaction studies with JENTADUETO have not been performed; however, such studies have been conducted with the individual linagliptin and metformin components of JENTADUETO.

Co-administration of multiple doses of linagliptin (10 mg once daily) and metformin hydrochloride (850 mg twice daily) did not meaningfully alter the pharmacokinetics of either linagliptin or metformin in healthy volunteers.

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

In Vitro Assessment of Drug Interactions: Linagliptin is metabolized by the CYP isozyme CYP 3A4 to one pharmacologically inactive metabolite. In *in vitro* studies, linagliptin is a weak competitive and a weak to moderate inhibitor of CYP3A4. Linagliptin is not an inhibitor of CYP 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 or 4A11 and is not an inducer of CYP 1A2, CYP 2B6 or CYP 3A4.

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

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

Metformin hydrochloride
The simultaneous administration of JENTADUETO and a sulfonylurea could produce a hypoglycemic reaction, especially if they are given in patients already receiving other drugs which, themselves, can potentiate the effect of sulfonylureas. These drugs can be: long-acting sulfonamides, tubercolostatics, phenylbutazone, clofibrate, monoamine oxidase inhibitors, salicylates, probenecid and propranolol.

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of JENTADUETO and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Drug-Drug Interactions
Linagliptin
In Vivo Assessment of Drug Interactions: Linagliptin had no clinically relevant effect on the pharmacokinetics of metformin, glibenclamide, simvastatin, pioglitazone, warfarin, digoxin or oral contraceptives providing *in vivo* evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-glycoprotein, and organic cationic transporter (OCT). No dose adjustment of linagliptin is recommended based on results of the described pharmacokinetic studies.

Metformin: Co-administration of multiple three-times-daily doses of 850 mg metformin with a supratherapeutic dose of 10 mg linagliptin once daily did not alter the pharmacokinetics of linagliptin or metformin in healthy volunteers in a clinically meaningful way. Therefore, linagliptin is not an inhibitor of OCT-mediated transport.

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

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

Ritonavir: A study was conducted to assess the effect of ritonavir, a potent inhibitor of P-glycoprotein and CYP3A4, on the pharmacokinetics of linagliptin. Co-administration of a single 5 mg oral dose of linagliptin and 200 mg twice daily oral doses of ritonavir for three days increased the AUC and C_{max} of linagliptin approximately twofold and threefold, respectively. Simulations of steady state plasma concentrations of linagliptin with and without ritonavir indicated that the increase in exposure will not be associated with an increased accumulation. These changes in linagliptin pharmacokinetics were not considered to be clinically relevant. Therefore, clinically relevant interactions would not be expected with other P-glycoprotein/CYP3A4 inhibitors and dose adjustment is not required.

Rifampicin: A study was conducted to assess the effect of rifampicin, a potent inducer of P-glycoprotein and CYP3A4, on the pharmacokinetics of 5 mg linagliptin. Co-administration of linagliptin with rifampicin, resulted in a 39.6% and 43.8% decreased linagliptin steady state AUC and C_{max}, respectively, and about 30% decreased DPP-4 inhibition at trough. Thus, full efficacy might not be achieved with long term co-administration of linagliptin and rifampicin (or other strong P-gp/CYP3A4 inducers). The physician should closely monitor glucose. In cases of insufficient efficacy, the physician should consider either a change of the P-gp/CYP3A4 inducer to a non P-gp/CYP3A4 inducing compound or a change of JENTADUETO to another oral antidiabetic (see WARNINGS AND PRECAUTIONS).

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

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

Simvastatin: Multiple daily doses of linagliptin had a minimal effect on the steady state pharmacokinetics of simvastatin, a sensitive CYP3A4 substrate, in healthy volunteers. Following administration of 10 mg linagliptin concomitantly with 40 mg of simvastatin daily for 6 days, the plasma AUC of simvastatin was increased by 34%, and the plasma C_{max} by 10%. Therefore, linagliptin is unlikely to cause clinical meaningful interactions with simvastatin (or other statins which share similar elimination pathways). Linagliptin is considered to be a weak inhibitor of CYP3A4-mediated metabolism, and dosage adjustment of concomitantly administered substances metabolised by CYP3A4 is considered unnecessary.

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

Metformin hydrochloride
Glyburide: In a single-dose interaction study in type 2 diabetes patients, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood

levels and pharmacodynamics effects, makes the clinical significance of this interaction uncertain.

Furosemide: A single-dose study, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine: A single-dose, metformin-nifedipine drug interaction study in healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic Drugs: Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such an interaction has been observed between metformin and oral cimetidine in normal healthy volunteers in both single and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC was observed. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics.

Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of JENTADUETO and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Levothyroxine: Levothyroxine can reduce the hypoglycemic effect of metformin. Monitoring of blood glucose levels is recommended, especially when thyroid hormone therapy is initiated, changed, or stopped (see WARNINGS AND PRECAUTIONS), and metformin dosage adjusted as necessary (see DOSAGE AND ADMINISTRATION).

Anticoagulant: Elimination rate of the anticoagulant phenprocoumon has been reported to be increased by 20% when used concurrently with metformin. Therefore, a close monitoring of the International Normalized Ratio (INR) is recommended in patients concurrently administering metformin and phenprocoumon or other antivitamin K anticoagulants (see WARNINGS AND PRECAUTIONS). In such cases, an important increase of prothrombin time may occur upon cessation of JENTADUETO therapy, with an increased risk of hemorrhage.

Other: Certain drugs tend to produce hyperglycemia and may lead to a loss of glycemic control. These include thiazide and other diuretics, corticosteroids, phenothiazines, thyroid hormone replacement drugs e.g. levothyroxine,estrogens, estrogen plus progestogen, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, isoniazid, and beta-2-agonists. ACE-inhibitors may decrease the blood glucose levels. When such drugs are administered to patients receiving JENTADUETO, the patient should be closely observed to maintain adequate glycemic control (see WARNINGS AND PRECAUTIONS).

Diuretics, especially loop diuretics, may increase the risk of lactic acidosis due to their potential to decrease renal function (see DOSAGE AND ADMINISTRATION).

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

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

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

Metformin hydrochloride
Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Drug-Lifestyle Interactions
Effects of Smoking, Alcohol, and Diet: The effects of smoking, diet, and alcohol use on the pharmacokinetics of JENTADUETO have not been specifically studied. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking JENTADUETO, since alcohol intake potentiates the effect of metformin on lactate metabolism (see CONTRAINDICATIONS). The risk of lactic acidosis is increased in acute alcohol intoxication, particularly in case of fasting or malnutrition or hepatic insufficiency. It is recommended that consumption of alcohol and alcohol-containing medicinal product be avoided.

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

The available doses of JENTADUETO are 2.5/500 mg, 2.5/ 850 mg and 2.5/1000 mg twice daily. The dosage should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 5 mg linagliptin and 2000 mg metformin hydrochloride.

JENTADUETO should be given twice daily with meals with gradual dose escalation to reduce the gastrointestinal undesirable effects associated with metformin. Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin-containing products in patients with renal impairment. Maximum daily dose of linagliptin and metformin, as single components, in patients with an eGFR ≥30 mL/min/1.73 m^2 to <45 mL/min/1.73 m^2 is 5 mg and 1000 mg, respectively.

If glycemic control is found to be reduced, alternative treatments should be considered.

Concomitant Use with Medication(s) that May Decrease Renal Function

Caution should be exercised when using concomitant medication(s) that may decrease renal function (like diuretics, particularly loop diuretics) or may interfere with the disposition of metformin, such as cationic drugs, that are eliminated by renal tubular secretion, due to the increased risk of developing lactic acidosis during co-administration (see DRUG INTERACTIONS).

Recommended Dose and Dosage Adjustment

For patients inadequately controlled on metformin monotherapy

For patients not adequately controlled on metformin alone, the usual starting dose of JENTADUETO 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, JENTADUETO should be initiated at the dose of linagliptin and metformin already being taken.

For patients inadequately controlled on dual combination therapy with metformin and a sulfonylurea

The dose of JENTADUETO 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 JENTADUETO is used in combination with a sulfonylurea; a lower dose of the sulfonylurea may be required to reduce the risk of hypoglycemia (see WARNINGS AND PRECAUTIONS).

For patients inadequately controlled on dual combination therapy with metformin and basal insulin

The dose of JENTADUETO 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 JENTADUETO is used in combination with basal insulin; a lower dose of the basal insulin may be required to reduce the risk of hypoglycemia (see WARNINGS AND PRECAUTIONS).

Renal Impairment: Renal function must be assessed prior to initiation of JENTADUETO and periodically and at least annually thereafter. In patients with eGFR <60 mL/min/1.73m^2, more intensive monitoring for glycemic biomarkers, renal biomarkers and signs and symptoms of renal dysfunction is recommended especially if the eGFR is less than 45 mL/min/1.73 m^2 (see WARNINGS AND PRECAUTIONS).

JENTADUETO is contraindicated in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2), end stage renal disease or patients on dialysis (see CONTRAINDICATIONS).

Initiation of JENTADUETO in patients with an eGFR ≥30 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2 is not recommended. In patients taking JENTADUETO whose eGFR later falls below 45 mL/min/1.73 m^2, assess the benefit and risk of continuing therapy and limit dose of the metformin to a maximum of 1000 mg daily. Discontinue JENTADUETO if the patient's eGFR later falls below 30 mL/min/1.73 m^2 (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

No dosage adjustment for JENTADUETO is necessary in patients with mild (eGFR ≥60 mL/min/1.73 m^2 to <90 mL/min/1.73 m^2) to moderate renal impairment (eGFR ≥45 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2).

Discontinuation for iodinated contrast imaging procedures
Discontinue JENTADUETO at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR ≥30 to <60 mL/min/1.73 m^2; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart JENTADUETO if renal function is acceptable and found to be stable (see WARNINGS AND PRECAUTIONS).

Hepatic Impairment: Use of JENTADUETO in patients with severe hepatic impairment is contraindicated and should not be used in patients with clinical or laboratory evidence of hepatic disease (see CONTRAINDICATIONS). Metformin use in patients with impaired hepatic function has been associated with some cases of lactic acidosis (see WARNINGS AND PRECAUTIONS).

Geriatrics (≥65 years of age): JENTADUETO should be used with caution in patients 65 years and older. Regular assessment of renal function is necessary. As metformin is excreted via the

kidney, and elderly patients are more likely to have decreased renal function associated with aging and be at risk of developing lactic acidosis (see WARNINGS AND PRECAUTIONS).

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

Missed Dose

If a dose of JENTADUETO is missed, it should be taken as soon as the patient remembers. If he/she does not remember until it is time for the next dose, the missed dose should be skipped and return to the regular schedule. Two doses of JENTADUETO should not be taken at the same time.

OVERDOSAGE

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

Linagliptin

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

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

Metformin hydrochloride

Available information concerning treatment of a massive overdosage of metformin hydrochloride is very limited. It would be expected that adverse reactions of a more intense character including epigastric discomfort, nausea and vomiting followed by diarrhea, drowsiness, weakness, dizziness, malaise and headache might be seen. Should those symptoms persist, lactic acidosis should be excluded. The drug should be discontinued and proper supportive therapy instituted.

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases (see WARNINGS AND PRECAUTIONS). Metformin is dialyzable with a clearance of up to170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

Pancreatitis may occur in the context of a metformin overdose (see WARNINGS AND PRECAUTIONS).

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

JENTADUETO targets three core defects of type 2 diabetes which are: decreased insulin synthesis and release, increased hepatic glucose production and decreased insulin sensitivity.

Linagliptin

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

Metformin hydrochloride

Metformin is a biguanide derivative producing an antihyperglycemic effect which can only be observed in man or in the diabetic animal and only when there is insulin secretion. Metformin, at therapeutic doses, does not cause hypoglycemia when used alone in man or in the non-diabetic animal, except when using a near lethal dose. Metformin has no effects on the pancreatic beta cells. The mode of action of metformin is not fully understood. It has been postulated that metformin might potentiate the effect of insulin or that it might enhance the effect of insulin on the peripheral receptor site. This increased sensitivity seems to follow an increase in the number of insulin receptors on cell surface membranes.

Pharmacodynamics

Linagliptin

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

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

Metformin hydrochloride
Few data are available on the relationship between pharmacodynamics and pharmacokinetics, and therefore the effect of metformin on glucose control cannot be predicted from pharmacokinetic data alone. Tissue concentrations of metformin in the dual target sites of the liver and muscle appear to be more informative, and the deep metformin compartment supplying these tissues is critical and related to plasma concentrations. This view substantiates the clinical observation that the glucose-lowering action of metformin takes time to be fully expressed and also that activity is not lost immediately on drug withdrawal.

Pharmacokinetics

In a bioequivalence study of JENTADUETO 2.5 mg/500 mg (linagliptin/metformin hydrochloride), both the linagliptin component and the metformin component were bioequivalent to 2.5 mg linagliptin and 500 mg metformin hydrochloride (GLUCOPHAGE€) co-administered as individual tablets in healthy subjects.

Because JENTADUETO dosage formats (i.e. 2.5 mg/500 mg, 2.5 mg/850 mg and 2.5 mg/1000 mg linagliptin/metformin hydrochloride) are proportionally formulated, demonstration of bioequivalence of JENTADUETO (2.5 mg/500 mg) to its individual components confers bioequivalence of the other strengths of JENTADUETO to its components.

The comparative bioavailability data for linagliptin and metformin following administration of 1 x 2.5 mg/500 mg as JENTADUETO (linagliptin/metformin hydrochloride) tablets or as the free combination of linagliptin and metformin (GLUCOPHAGE€) are shown in Table 6.

Table 6 Pharmacokinetics Parameters from Comparative Bioavailability Studies

Linagliptin (1 x 2.5 mg as either JENTADUETO or linagliptin†) Geometric Mean Arithmetic Mean (CV%) From measured data				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_{0-72} (nmol*h/L)	181 188 (27.0)	181 188 (26.9)	99.9	96.6-103.3
AUC_{0-inf} (nmol*h/L)	279 292 (30.4)	281 294 (31.2)	99.2	95.6-103.0
C_{max} (nmol/L)	5.3 5.5 (27.4)	5.4 5.6 (27.6)	98.1	94.4-101.9
T_{max} ** (h)	3.0 (0.7-8.0)	3.0 (1.0-8.0)		
$T_{½}$ § (h)	49.3 (20.1)	50.1 (16.6)		
Metformin (1 x 500 mg as either JENTADUETO or GLUCOPHAGE metformin hydrochloride €) Geometric Mean Arithmetic Mean (CV%) From measured data				
Parameter	**Test***	**Reference€**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_t (ng.h/mL)	6909.6 7079.7 (24)	6605.3 6808.3 (25)	104.6	100.9-108.5
AUC_{inf} (ng.h/mL)	7027.3 7198.8 (23)	6720.8 6923.8 (24)	104.6	101.0-108.3
C_{max} (ng/mL)	879.1 901.8 (29)	746.5 770.5 (25)	117.8	110.5-125.5
T_{max}** (h)	2.0 (69)	3.0 (39)		
$T_{½}$ § (h)	8.9 (43)	8.4 (31)		

* JENTADUETO (linagliptin/metformin hydrochloride) 2.5 mg/500 mg
†linagliptin 2.5 mg tablet
€ GLUCOPHAGE (metformin hydrochloride) 500 mg tablet, by Sanofi-Aventis Canada Inc.
§ Arithmetic mean only (CV%)
** Median (range) only

Administration of JENTADUETO 2.5 mg/1000 mg with a high-calorie, high-fat meal, resulted in no significant change in overall exposure of linagliptin compared to fasted administration. With metformin there was no significant change in AUC, however the mean peak plasma concentration of metformin was decreased by 18% when administered with food. A delayed time to peak plasma concentrations by 2 hours was observed for metformin under fed conditions.

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

Absorption:

Linagliptin

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

Metformin hydrochloride

Metformin absorption is relatively slow and may extend over about 6 hours.

Distribution:

Linagliptin

As a result of tissue binding, the mean apparent volume of distribution at steady state following a single 5 mg intravenous dose of linagliptin to healthy subjects is approximately 1110 litres, indicating that linagliptin extensively distributes to the tissues. Plasma protein binding of linagliptin is concentration-dependent, decreasing from about 99% at 1 nmol/L to 75-89% at ≥30 nmol/L, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin. At high concentrations (>30 nM) the plasma protein binding of linagliptin was constant with a moderate bound fraction between 70-80%. Plasma binding was not altered in patients with renal or hepatic impairment.

Metformin hydrochloride

Plasma protein binding is negligible. Metformin 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 (Vd) ranged between 63-276 l.

Metabolism:

Linagliptin

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

Metformin hydrochloride

Metformin is not metabolized. Its main sites of concentration are the intestinal mucosa and the salivary glands. The plasma concentration at steady state ranges about 1 to 2 mcg/mL. Certain drugs may potentiate the effects of metformin (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Excretion:

Linagliptin

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

Metformin hydrochloride
The drug is excreted in urine at high renal clearance rate of about 450 mL/min. The initial elimination of metformin is rapid with a half-life varying between 1.7 and 3 hours. The terminal elimination phase accounting for about 4 to 5% of the absorbed dose is slow with a half-life between 9 and 17 hours.

Special Populations and Conditions

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

Geriatrics (≥65 years of age):

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

Metformin hydrochloride
Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients.

Limited data from controlled pharmacokinetic studies of metformin hydrochloride in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to 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 (see WARNINGS AND PRECAUTIONS).

JENTADUETO treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced (see WARNINGS AND PRECAUTIONS).

Gender:

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

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.

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

Metformin hydrochloride
No studies of metformin pharmacokinetic parameters according to race have been performed.

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

Renal Impairment: JENTADUETO is contraindicated in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) (see CONTRAINDICATIONS).

Linagliptin
A multiple-dose, open-label study was conducted to evaluate the pharmacokinetics of linagliptin (5 mg dose) in patients (n=6 in each group) with mild and moderate renal impairment compared to subjects with normal renal function. A single-dose pharmacokinetic study of linagliptin was conducted in patients with severe renal impairment (n=6) and ESRD (n=6). The studies included patients with renal impairment classified on the basis of creatinine clearance as mild (50 to 80 mL/min), moderate (30 to 50 mL/min), and severe (<30 mL/min), as well as patients with end-stage renal disease on hemodialysis. In addition, patients with T2DM and severe renal impairment (n=10) were compared to T2DM patients with normal renal function (n=11) in a multiple-dose study. After a single oral dose of linagliptin, exposure was 1.2 to 1.6-fold higher for patients with renal impairment (with or without T2DM) than for subjects with normal renal function (with or without T2DM).

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

Metformin hydrochloride
In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Hepatic Impairment: Use of JENTADUETO in patients with severe hepatic impairment is contraindicated and should not be used in patients with clinical or laboratory evidence of hepatic disease (see CONTRAINDICATIONS).

Linagliptin
In patients with mild or moderate hepatic insufficiency (according to the Child-Pugh classification), mean AUC and C_{max} of linagliptin were similar to healthy matched controls following administration of multiple 5 mg doses of linagliptin. No dose adjustment for linagliptin is required for patients with mild or moderate hepatic impairment. While Phase I data showed no clinical relevant effect of severe hepatic impairment on linagliptin pharmacokinetics following administration of single 5 mg dose, use in these patients is not recommended due to lack of clinical experience.

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

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

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

JENTADUETO tablets 2.5 mg/500 mg, are light yellow, oval biconvex film-coated tablets containing, 2.5 mg of linagliptin and 500 mg of metformin hydrochloride. JENTADUETO tablets are debossed with “D2/500” on one side and the Boehringer Ingelheim logo on the other side. They are supplied as blisters of 60.

JENTADUETO tablets 2.5 mg/850 mg, are light orange, oval biconvex film-coated tablets containing, 2.5 mg of linagliptin and 850 mg of metformin hydrochloride. JENTADUETO tablets are debossed with “D2/850” on one side and the Boehringer Ingelheim logo on the other side. They are supplied as blisters of 60.

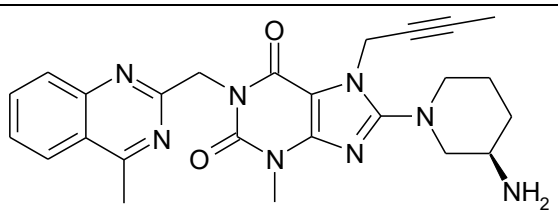
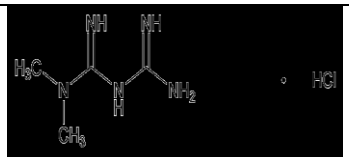
JENTADUETO tablets 2.5 mg/1000 mg, are light pink, oval biconvex film-coated tablets containing, 2.5 mg of linagliptin and 1000 mg of metformin hydrochloride. JENTADUETO tablets are debossed with “D2/1000” on one side and the Boehringer Ingelheim logo on the other side. They are supplied as blisters of 60.

Non-medicinal ingredients: arginine, colloidal silicon dioxide, copovidone, magnesium stearate, maize starch. In addition, the film coating contains the following inactive ingredients: hypromellose, iron oxide red, iron oxide yellow, propylene glycol, talc, titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name:	linagliptin	metformin hydrochloride
Chemical Name:	1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl)methyl]-	*N,N*-dimethyl biguanide hydrochloride
Molecular formula:	$C_{25}H_{28}N_8O_2$,	$C_4H_{11}N_5HCl$
Molecular mass:	472.54 g/mol	165.63 g/mol
Structural formula:		
Physicochemical properties:	White to yellowish crystalline solid substance, very slightly soluble in water, soluble in methanol, sparingly soluble in ethanol, very slightly soluble in isopropanol and in acetone.	White to off-white crystalline compound, freely soluble in water, practically insoluble in acetone, ether and chloroform.
pKa:	$pKa_1 = 8.6$; $pKa_2 = 1.9$	pKa 12.4
Partition Co-efficient	Log P = 1.7 (free base); Log D (pH 7.4) = 0.4	pH of 1% aqueous solution is 6.68
Melting Temperature:	202-209°C	218-220°C

CLINICAL TRIALS

The co-administration 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 or insulin.

There have been no clinical efficacy studies conducted with JENTADUETO; however, bioequivalence of JENTADUETO to co-administered linagliptin and metformin hydrochloride tablets was demonstrated in healthy subjects.

Study Demographics and Trial Design

Table 7 Summary of Patient Demographics for Clinical Trials in Specific Indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender (% F/M)
Add on Combination Therapy with Metformin					
1218.17	Multicentre, randomized, double-blind, placebo-controlled	Linagliptin 5 mg or placebo Oral, 24 weeks	Total: 701 Linagliptin : 524 Placebo: 177	56 (21-79)	46/54
1218.46	Multicentre, randomized, double-blind, placebo controlled	Linagliptin 2.5 mg and metformin (500 mg or 1000 mg) bid, or metformin monotherapy (500 mg or 1000 mg) bid, or Linagliptin monotherapy 5 mg qd or placebo Oral, 24 weeks	Total: 791 Lina 2.5 mg + Met 500 mg:143 Lina 2.5 mg +Met 1000 mg:143 Placebo: 72 Lina 5 mg: 142 Met 500 mg: 144 Met 1000 mg:147	55 (25-80)	46/54
1218.62	Multicentre, randomized, double-blind, placebo-controlled	Linagliptin 2.5 mg bid, or Linagliptin 5 mg qd, placebo Oral, 12 weeks	Total: 491 Lina 2.5 mg bid: 223 Lina 5 mg qd: 224 Placebo 44	59 (26-80)	43/57
1218.20	Multicentre, randomized, double-blind, active-controlled	Linagliptin 5 mg or glimepiride (forced titration from 1 mg to max. 4 mg) Oral, 52 weeks	Total: 1560 Linagliptin : 779 Glimepiride: 781	60 (28-80)	40/60
Add on Combination Therapy with Metformin and a Sulfonylurea					
1218.18	Multicentre, randomized, double-blind, placebo-controlled	Linagliptin 5 mg or placebo Oral, 24 weeks	Total: 1058 Linagliptin: 793 Placebo: 265	58 (23-79)	53/47

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender (% F/M)
Add on Combination Therapy with Insulin					
1218.36	Multicentre, randomized, double-blind, placebo-controlled	Linagliptin 5 mg or placebo Oral, 52 weeks	Total: 1261 Linagliptin: 631 Placebo: 630	60 (22-91)	48/52

Study Results

Linagliptin as add-on to metformin therapy

BI Study 1218.17

The efficacy and safety of linagliptin 5 mg in combination with metformin was evaluated in a double blind placebo controlled study of 24 weeks duration. Linagliptin provided significant improvements in HbA_{1c}, fasting plasma glucose (FPG), 2-hour post-prandial glucose (PPG) and a greater portion of patients (28%) achieved a target HbA_{1c} of <7.0%, compared to placebo (11%) (Table 8). Body weight did not differ significantly between the groups.

Table 8 Glycemic Parameters at Final Visit (Placebo-Controlled Study) for Linagliptin in Combination with Metformin (BI Study 1218.17)

	Linagliptin 5 mg + Metformin	Placebo + Metformin
HbA_{1C} (%)	**n = 513**	**n =175**
Baseline (mean)	8.09	8.02
Change from baseline (adjusted mean)	-0.49	0.15
Difference from placebo + metformin (adjusted mean) (95% CI)	-0.64 (-0.78, -0.50)	--
Patients (%) achieving HbA_{1C} <7%	145 (28.3)	20 (11.4)
FPG (mmol/L)	**n = 495**	**n = 159**
Baseline (mean)	9.39	9.10
Change from baseline (adjusted mean)	-0.59	0.58
Difference from placebo + metformin (adjusted mean) (95% CI)	-1.17 (-1.52, -0.83)	--
2-hour PPG (mmol/L)	**n = 78**	**n = 21**
Baseline (mean)	15.0	15.22
Change from baseline (adjusted mean)	-2.71	1.01

	Linagliptin 5 mg + Metformin	Placebo + Metformin
Difference from placebo + metformin (adjusted mean) (95% CI)	-3.72 (-5.26, -2.20)	--

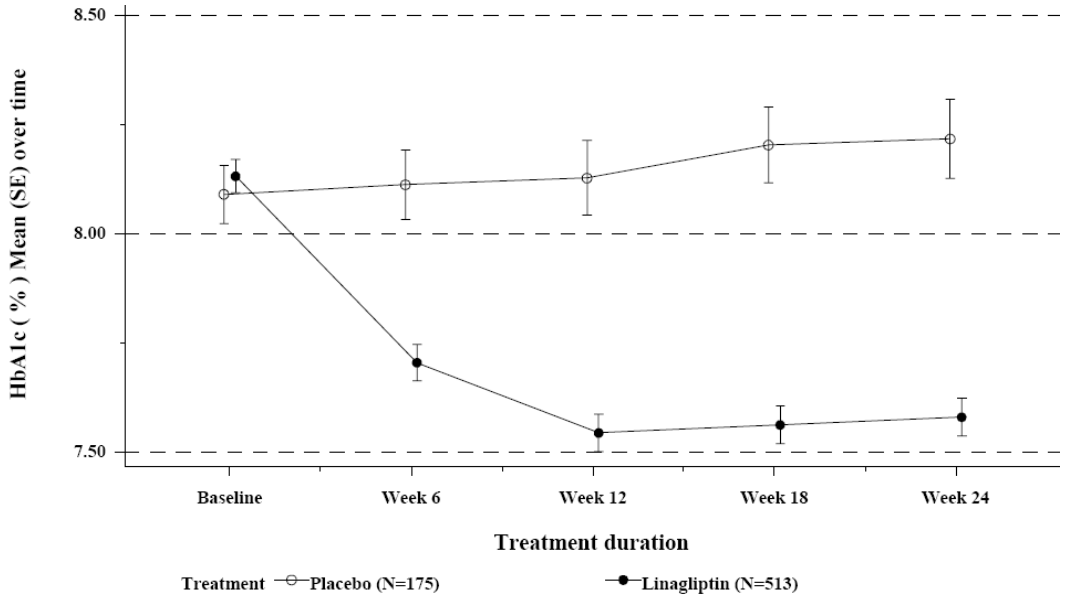


Figure 1 Mean HbA_{1C} (%) over 24 Weeks with Linagliptin/Metformin and Placebo/ Metformin in Patients with Type 2 Diabetes (BI Study 1218.17, add-on to metformin patients)

BI Study 1218.46

In a 24-week placebo-controlled factorial study, linagliptin 2.5 mg twice daily in combination with metformin (500 mg or 1000 mg twice daily) provided significant improvements in glycemic parameters compared with either monotherapy as summarized in Table 9 (mean baseline HbA_{1c} 8.65%) and Figure 2.

Table 9 Glycemic 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
HbA_{1c} (%)						
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 HbA_{1c} <7%	7 (10.8)	14 (10.4)	27 (19.1)	42 (30.7)	43 (31.2)	76 (54.3)
FPG (mmol/L)						
Number of patients	**n = 61**	**n = 134**	**n = 136**	**n = 135**	**n = 132**	**n = 136**
Baseline (mean)	11.3	10.8	10.6	11.1	10.6	10.9
Change from baseline (adjusted mean)	0.6	-0.5	-0.9	-1.8	-1.8	-2.7
Difference from placebo (adjusted mean) (95% CI)	--	-1.0 (-1.7, -0.3)	-1.4 (-2.1, -0.8)	-2.4 (-3.1, -1.7)	-2.3 (-3.0, -1.7)	-3.3 (-4.0, -2.6)

* Total daily dose of linagliptin is equal to 5 mg

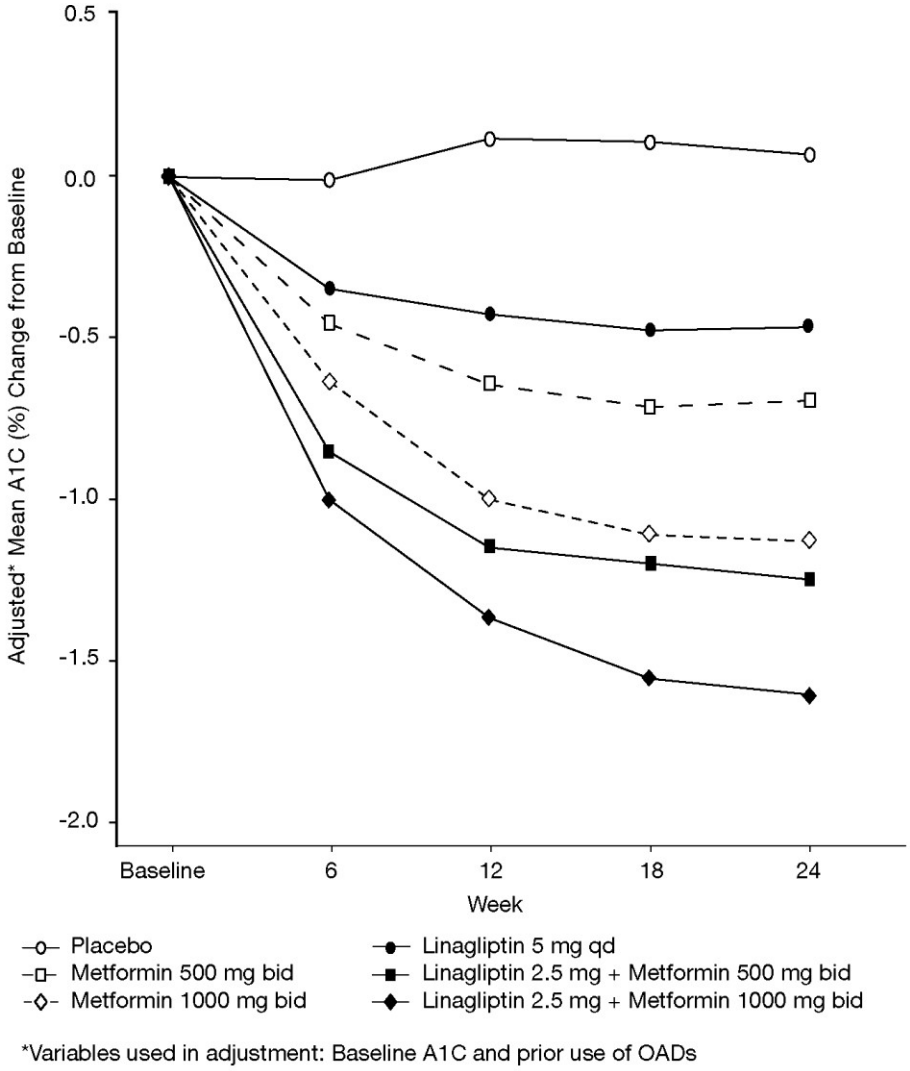


Figure 2 Adjusted Mean Change from Baseline for HbA_{1C} (%) over 24 Weeks with Linagliptin and Metformin, Alone and in Combination in Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Diet and Exercise - FAS completers (LOCF).

Mean reductions from baseline in HbA_{1c} were generally greater for patients with higher baseline HbA_{1c} values. There were no differences in the body weight between the treatment groups. The incidence of hypoglycemia was similar across treatment groups (placebo 1.4%, linagliptin 5 mg 0%, metformin 2.1%, and linagliptin 2.5 mg plus metformin twice daily 1.4%).

BI Study 1218.62

The efficacy and safety of linagliptin 2.5 mg twice daily versus 5 mg once daily in combination with metformin in patients with insufficient glycemic 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 glycemic parameters compared to placebo. Linagliptin 5 mg once daily and 2.5 mg twice daily provided comparable (CI: -0.07; 0.19), significant HbA_{1c} reductions of -0.80% (from baseline 7.98%), and -0.74% (from baseline 7.96%) compared to placebo (Table 10).

The observed incidence of hypoglycemia in patients treated with linagliptin was similar to placebo (3.1% 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.

Table 10 Glycemic Parameters at Final Visit (12-Week Study) for Linagliptin 2.5 mg bid and 5 mg qd in Combination with Metformin (BI Study 1218.62)

	Placebo + Metformin	**Linagliptin 2.5 mg bid + Metformin**	**Linagliptin 5 mg qd + Metformin**
HbA_{1C} (%)	**n = 43**	**n = 214**	**n = 221**
Baseline (mean)	7.92	7.96	7.98
Change from baseline (adjusted mean)	0.28	-0.46	-0.52
Difference between treatments (95% CI) : Lina 5 mg qd - Placebo Lina 2.5 mg bid - Placebo Lina 2.5 mg bid - Lina 5 mg qd		-0.74 (-0.97, -0.52) 0.06 (-0.07, 0.19)	-0.80 (-1.02, -0.58)
FPG (mmol/L)	**n = 40**	**n = 203**	**n = 213**
Baseline (mean)	9.12	9.05	9.18
Change from baseline (adjusted mean)	-0.19	-0.95	-1.18
Difference between treatments (95% CI) : Lina 5 mg qd - Placebo Lina 2.5 mg bid - Placebo Lina 2.5 mg bid - Lina 5 mg qd		-0.76 (-1.26, -0.26) 0.22 (-0.06, 0.51)	-0.99 (-1.48, -0.49)

Linagliptin as add-on to a combination of metformin and a sulfonylurea therapy

BI Study 1218.18

A placebo-controlled study of 24 weeks in duration was conducted to evaluate the efficacy and safety of linagliptin 5 mg compared to placebo, in patients not sufficiently treated with a combination with metformin and a sulfonylurea. Linagliptin provided significant improvements in HbA_{1c}, fasting plasma glucose (FPG), and 2-hour post-prandial glucose (PPG) and a greater portion of patients (31%) achieved a target HbA_{1c} of <7.0% compared to placebo (9%) (Table 11). Body weight did not differ significantly between the groups.

Table 11 Glycemic Parameters at Final Visit (24-Week Study) for Linagliptin in Combination with Metformin and Sulfonylurea (BI Study 1218.18)

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

SU = sulfonylurea

Linagliptin as add-on to insulin therapy

BI Study 1218.36

The efficacy and safety of linagliptin 5 mg as add-on therapy to a stable dose of basal insulin regimen was evaluated in a total of 1261 patients with type 2 diabetes mellitus inadequately controlled (HbA_{1c} level of ≥7.0 to ≤10%) on insulin alone or in combination with other antihyperglycemic agents in a randomized double-blind placebo-controlled study of at least 52 weeks duration. Patients using prandial insulin alone or in pre-mixed formulations or insulin delivered by pump were not included in this study. The mean treatment difference in HbA_{1c} between linagliptin versus placebo from baseline to Week 24 (LOCF) was -0.65% (95% CI -

0.74, -0.55; p<0.0001) from a mean baseline HbA_{1c} of 8.3%. Linagliptin also showed modest but significant improvements in fasting plasma glucose (FPG) of -0.62 mmol/L (95% CI -0.95%, -0.90, -0.35; p<0.0001) compared to placebo, and a greater portion of patients achieved a target HbA_{1c} of <7.0%, compared to placebo. Body weight did not differ significantly between the groups. After 24 weeks of treatment, the mean daily insulin dose at baseline was 42 units in patients treated with linagliptin and 40 units in placebo-treated patients. The mean change from baseline to Week 24 in daily dose of insulin was 1.3 IU in the placebo group and 0.6 IU in the linagliptin group.

Based on subgroup analyses of background antidiabetic medications (Table 12), there was a slightly greater efficacy in patients taking insulin and metformin than insulin alone. Of 197 patients on a background of insulin alone (no concomitant oral antidiabetic agents), the mean placebo-adjusted change from baseline in HbA_{1c} at Week 24 (LOCF) was -0.54 (p<0.0001). Based on a subgroup analysis of 932 patients on a background of insulin plus metformin only, the mean placebo-adjusted reduction from baseline in HbA_{1c} at Week 24 (LOCF) was -0.67 (p<0.0001).

Table 12 Glycemic Parameters in Placebo-Controlled Study for Linagliptin in Combination with Insulin Alone or Insulin with Metformin* at 24 Weeks

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

*Full analysis population using last observation carried forward (LOCF)
[1] ANCOVA model includes treatment, continuous baseline HbA1c and renal impairment category
[2] ANCOVA model includes treatment, continuous baseline HbA1c, continuous baseline FPG and renal impairment category

Linagliptin as add-on to metformin in comparison with glimepiride

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

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

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

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

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

standard of care targeting regional standards for HbA_{1c}, CV risk factors and renal disease. The mean duration of study follow-up was 2.2 years. The proportion of subjects who completed the study was 98.7%.

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

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

Linagliptin, when added to standard of care, did not increase the risk of major adverse CV events or renal outcome events (Table 13 and Figure 3). There was no increased risk in hospitalization for heart failure which was an additional adjudicated endpoint observed compared to usual care without linagliptin in patients with T2D (Table 14 and Figure 4). Superiority to placebo was not demonstrated for any endpoint in hypothesis testing of 3-point MACE or other pre-specified CV endpoints.

Table 13 Major Adverse Cardiovascular Events (MACE) and Renal Outcome Events Reported in the CARMELINA Study

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

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

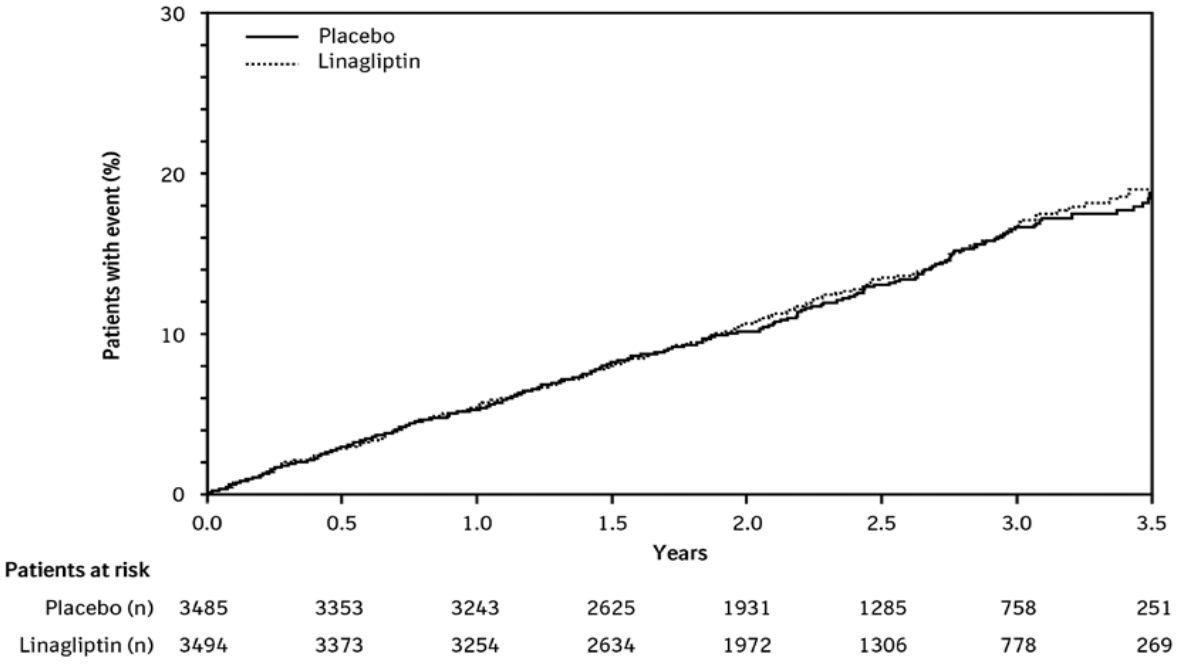


Figure 3 Time to First Occurrence of 3-Point MACE in CARMELINA

Table 14 Other Cardiovascular and Mortality Outcomes in the CARMELINA Study

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

Abbreviations: CV = cardiovascular; CI = confidence of interval

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

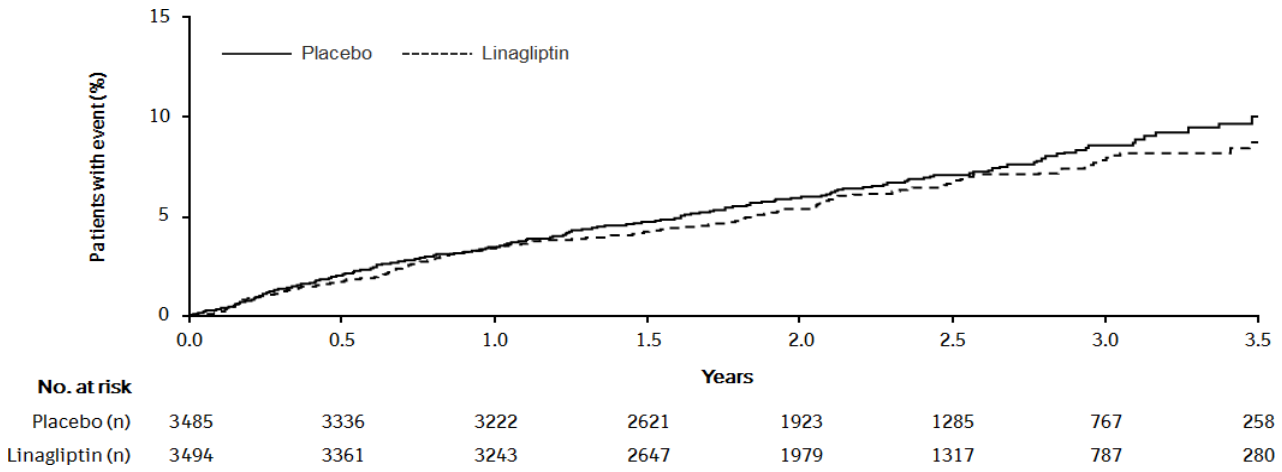


Figure 4 Kaplan-Meier Estimation of Time to First Hospitalisation for Heart Failure – TS

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

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

The study was designed to demonstrate non-inferiority of treatment with linagliptin in comparison with glimepiride (predominantly on metformin background treatment) for the primary CV endpoint which was the time to first occurrence of any of the following adjudication-confirmed components of the primary composite endpoint (3-point MACE): CV death, non-fatal myocardial infarction, or non-fatal stroke.

According to the pre-specified risk margin of 1.3, linagliptin did not increase the risk of major adverse CV events compared to glimepiride (Table 15). Linagliptin, when added to standard of care, was non-inferior compared to glimepiride. Superiority to glimepiride was not demonstrated for any endpoint in hypothesis testing of 3-point MACE.

Table 15 Major Adverse Cardiovascular Events (MACE) Reported in the CAROLINA Study

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

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

DETAILED PHARMACOLOGY

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

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

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

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

Metformin hydrochloride
Metformin absorption is relatively slow and may extend over about 6 hours. Animal studies with metformin, labelled with ^{14}C have shown that the drug is neither concentrated by liver cells nor is it excreted in the bile; it is concentrated in the intestinal mucosa and salivary glands. It has been shown that, following a 2 g dose of metformin, the blood level remains under 10 mcg/mL even at the peak, occurring 2 hours after absorption. During the experiments, metformin was shown to be devoid of any notable action in the body, apart from its specific metabolic activity.

In the healthy animal, metformin lowers blood sugar only at a nearly lethal dose. Different animal species are of unequal sensitivity. On the other hand, the animal with experimental diabetes is sensitive to a much lower dosage, providing some insulin is still secreted.

The antihyperglycemic action of metformin is probably mediated through insulin: Metformin improves the K co-efficient of glucose assimilation. Metformin improves the co-efficient of insulin efficiency.

In the obese diabetic with hyperinsulinemia, metformin is reported to normalize insulin output. This normalizing effect is concurrent to that of glycemia.

Metformin has little effect on liver glycogen of the healthy animal. In low and average doses, no change occurs. In high doses nearing lethal levels, liver glycogen decreases. This lowering precedes the fall in blood sugar. This reaction represents a defense mechanism tending to mobilize body reserves in order to combat hypoglycemia.

In the diabetic animal with a low liver glycogen reserve, the opposite occurs and metformin builds up glycogen stores of the liver. *In vitro*, on muscular tissue isolated in Warburg's apparatus, metformin increases glucose uptake by the muscle. This action follows an aerobic pathway. Even in high concentration, contrary to phenethyl-biguanide, metformin apparently does not block respiration or change carbohydrate metabolism via the anaerobic pathway.

Metformin is eliminated in faeces and urine. It is rapidly excreted by the kidneys in an unchanged form.

Renal clearance is 450 mL/minute; this appears to explain the absence of accumulation.

Metabolites of metformin have not been identified, neither by radio-active nor by chemical methods.

A single Rf spot is always present following radiochromatographic study of urine and always corresponds to that of pure metformin. Administration during 10 consecutive days has not shown any sign of accumulation.

Inhibition of glyconeogenesis has been observed in animals following its stimulation by fasting, cortisol, alcohol or other substrates such as alanine lactate or pyruvate. However, such an effect varies according to the type and dosage of the biguanide used, nutritional state of the animal species and design of experimental model. This inhibition of glyconeogenesis is observed only in the presence of insulin and it does not appear to play an important role in man.

Inhibition of intestinal absorption of sugars, which is not related to a malabsorption phenomenon, has been observed with biguanides under certain experimental conditions in animal and in man. In one study, a 20% retardation of galactose absorption was observed in man receiving metformin. However, such an effect of metformin could not be confirmed in another study in man.

Recent findings appear to indicate that most of the metabolic effects of the biguanides are exerted through a single mechanism, namely inhibition of fatty acid oxidation and of acetyl-CoA generation.

However, inhibition of insulin-stimulated lipogenesis which has also been observed appears to be due to the inhibition of acetyl-CoA carboxylase by the biguanides. Such an effect may explain, at least partly, the weight-reducing effect exerted by these drugs in obese diabetic patients.

TOXICOLOGY

JENTADUETO
General toxicity studies in rats for up to 13 weeks were performed with the combination of linagliptin and metformin. The only observed interaction between linagliptin and metformin was a reduction of body weight gain at doses of 2/800 and 4/800 mg/kg/day linagliptin/metformin. The no-observed-adverse-effect-level (0.5/100 mg/kg/day of linagliptin/metformin) derived from the 13-week rat study was 1.0 and 1.4 times human clinical exposure, respectively.

Co-administration of linagliptin and metformin to pregnant Wistar Han rats during the period of organogenesis was not teratogenic at doses up to 1/200 mg/kg/day linagliptin/metformin (1.5 and 3.3 times human clinical exposure, respectively). Increased incidences of fetal rib and scapula malformations and ossification delays were observed at doses of 500 or 1000 mg/kg/day metformin given alone or in combination with linagliptin (9.5 or 23.1 times human clinical exposure for metformin, respectively). These findings were metformin related and occurred in the presence of maternal toxicity which included decreases in body weight gain and related reductions in maternal food consumption.

The following data are findings in studies performed with linagliptin or metformin individually.

Linagliptin
Linagliptin was well tolerated and the minimum lethal dose after a single oral dose was 1000 mg/kg in rats and mice. Repeat oral dosing was associated with lethality/moribund euthanasia at ≥600 mg/kg (>3000 times human clinical exposure) in rats, 600 mg/kg (>3000 times human clinical exposure) in mice, 150 mg/kg (>1500 times human clinical exposure) in dogs and one monkey at 100 mg/kg (>750 times human clinical exposure). In dogs, a pseudo-allergic reaction occurred at ≥15 mg/kg and C_{max} 3690 nmol/L (>300 times human clinical C_{max}). The reaction was characterized by reddening and swelling of ears, circumocular region, as well as upper lips and vomiting. The reaction typically occurred 10 to 90 min post dose and then disappeared gradually and correlated reasonably with increases in circulating histamine concentrations. Linagliptin was associated with changes that appear secondary to irritation with high local concentrations of linagliptin in the GI tract after oral administration or in the biliary tract associated with excretion of drug. These ranged from minimal to slight epithelial hypertrophy/hyperplasia to ulcers and affected the gastro intestinal tract, gallbladder and biliary epithelium with or without peribiliary changes in mice (≥120 mg/kg, >400 times human clinical exposure), rats (≥300 mg/kg, >1500 times human clinical exposure), dogs (≥45 mg/kg, >200 times human clinical exposure) and monkeys (≥25 mg/kg, >100 times human clinical exposure). Linagliptin administration also results in metabolic effects that appear secondary to prolonged action of incretins as a result of DPP-4 inhibition. These include increased glycogen deposits in the hepatocytes of rat, mouse and monkey and decreases in cholesterol and triglycerides. The changes in the liver were not adverse at lower doses but at 300 mg/kg in the mouse and 100 mg/kg in the rat, there were either histological indication of adverse liver effects and/or increases in plasma markers for hepato-biliary perturbation. There were effects on kidney function or integrity in mouse, rat and monkey. In the monkey, there were no microscopic changes in the kidney but increases in plasma creatinine, kidney weight and urinary protein at ≥150 mg/kg (>1500 times human clinical exposure). In the rat, plasma creatinine and urea, increases in kidney weight and/or microscopic tubular damage were noted at ≥100 mg/kg. In the mouse, overt kidney toxicity was evident at 600 mg/kg. Linagliptin is an inducer of phospholipidosis in the rat. At 600 mg/kg, foam cells in liver, lung, lymph nodes, spleen, thymus and bone marrow were noted. Also in the rat at doses of ≥100 mg/kg, foci of foam cells were noted in the lung and at 60 mg/kg (approximately 400 times human clinical exposure) in the carcinogenicity study, there was an increased incidence of cholesterol cleft granuloma. There were no indications of effects on the immune system at doses up to 100 mg/kg (approximately 800 times human clinical exposure) for 52 weeks in the monkey, at doses up to 300 mg/kg (approximately 1800 times human clinical exposure) for 26 weeks in the rat, or in the mouse at 600 mg/kg (approximately 3300 times human clinical exposure) for 13 weeks. Increased apoptosis in the thymus, spleen and lymph nodes in rats and monkeys occurred at high doses and were attributed to stress and non-specific toxicity. The NOAEL after 52 weeks dosing was 10 mg/kg/day in the monkey and 30 mg/kg/day in a 26 week study in rats. At these doses, AUC values were 40 times human clinical exposure in the monkey and 66 times in the rat.

Carcinogenicity

Linagliptin

A two-year carcinogenicity study was conducted in male and female rats given oral doses of linagliptin of 6, 18, and 60 mg/kg/day. There was no increase in the incidence of tumors in any organ up to 60 mg/kg/day. This dose results in exposures approximately 400 times the human exposure at the maximum recommended daily adult human dose (MRHD) of 5 mg/day based on AUC comparisons. A two-year carcinogenicity study was conducted in male and female mice given oral doses of 8, 25 and 80 mg/kg/day. There was no evidence of a carcinogenic potential up to 80 mg/kg/day, approximately 240 times human clinical exposure.

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 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.

Genotoxicity

Linagliptin

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

Metformin hydrochloride

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.

Reproduction Toxicity

Linagliptin

In rat fertility studies with oral gavage doses of 10, 30 and 240 mg/kg/day, males were treated for 4 weeks prior to mating and during mating; females were treated 2 weeks prior to mating through gestation day 6. No adverse effect on early embryonic development, mating, fertility, and bearing live young were observed up to the highest dose of 240 mg/kg/day (approximately 900 times human clinical exposure of 5 mg/day based on AUC comparisons).

In the studies on embryo-fetal development in rats and rabbits, linagliptin was not teratogenic at dosages up to and including 240 mg/kg/day (approximately 900 times human clinical exposure) in the rat and 150 mg/kg/day (approximately 1900 times human clinical exposure) in the rabbit.

In the rat, at 240 mg/kg minor maternal toxicity was noted and there was a slight increased resorption rate, slight retardation of skeletal ossification, and also slightly increased incidence of flat and thickened ribs. Administration of 25 and 150 mg/kg to pregnant rabbits resulted in decreased mean body weight gain and decreased food consumption at 150 mg/kg. At 150 mg/kg, linagliptin treatment was associated with intrauterine death, runts (fetuses weighing less than 65% of the weighted control mean values) and an increased incidence of visceral and skeletal variations. A NOAEL of 30 mg/kg/day (approximately 50 times human clinical exposure) and 25 mg/kg/day (approximately 80 times human clinical exposure) was derived for embryo-fetal toxicity in the rat and the rabbit, respectively.

In a pre and postnatal development toxicity study in rats, treatment of the pregnant dams (the F_0 generation) at 300 mg/kg (approximately 1500 times human clinical exposure) during gestation and lactation caused decreased maternal body weight gain and food consumption observed during gestation and lactation. The F1 generation of dams treated at 300 mg/kg also showed reduced body weight during lactation and weaning. Their physical postnatal development proceeded in a normal range, except for delayed descensus testis and delayed preputial separation. These effects correlated with reduced body weight and were attributed to general growth retardation. The NOAEL was 30 mg/kg for both maternal and offspring toxicity (approximately 50 times human clinical exposure).

Metformin hydrochloride
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.

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PART III: CONSUMER INFORMATION

Pr Jentadueto®
Linagliptin/Metformin Hydrochloride Tablets

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

ABOUT THIS MEDICATION

What the medication is used for:
JENTADUETO is used in addition to diet and exercise to improve blood sugar levels in adults with type 2 diabetes mellitus:
- in patients who are not controlled on metformin alone;
- in patients currently on linagliptin and metformin alone;
- in combination with a sulfonylurea, in patients who are not controlled on metformin and a sulfonylurea; OR
- in combination with insulin, in patients who are not controlled on metformin and insulin.

What it does:
JENTADUETO is a prescription medicine that contains 2 diabetes medicines, linagliptin and metformin. Together, these medicines help you to achieve better blood sugar control.

Linagliptin is a member of a class of medicines called DPP-4 inhibitors (dipeptidyl peptidase-4 inhibitors). Linagliptin helps to improve blood sugar levels when they are high, especially after a meal. Linagliptin also helps to decrease the amount of sugar made by the body.

Metformin is a member of the biguanide class of medicines. It helps to lower the amount of sugar made by the liver and helps to lower the amount of sugar your intestines absorb.

What is type 2 diabetes?
Type 2 diabetes is a condition in which your body does not make enough insulin, and/or does not use the insulin that your body produces as well as it should. When this happens, sugar (glucose) builds up in the blood. This can lead to serious problems.

When it should not be used:
Do not take JENTADUETO if you:
- are allergic (hypersensitive) to linagliptin, metformin or any of the ingredients in JENTADUETO. See "What the non-medicinal ingredients are";
- have type 1 diabetes (your body does not produce any insulin);
- have liver or kidney problems;
- have a history of lactic acidosis;
- have metabolic acidosis (including diabetic ketoacidosis, history of ketoacidosis or lactic acidosis – too much acid in the blood);
- are going to get or receive an injection of dye or contrast agent for an x-ray procedure. Talk to your physician or pharmacist about when to stop JENTADUETO and when to start again;
- are stressed, have severe infections, are experiencing trauma, prior to surgery or during the recovery phase;
- have severe heart problems or heart failure;
- have a lack of oxygen in the blood. This is called hypoxemia. This can happen when you have conditions that affect your heart or breathing;
- are dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea, or sweat a lot with activity or exercise and do not drink enough fluids;
- drink a lot of alcohol, regularly or occasionally (binge drinking);
- are breastfeeding (nursing a child);
- are pregnant or planning to become pregnant.

What the medicinal ingredients are:
Linagliptin and metformin hydrochloride

What the important non-medicinal ingredients are:
JENTADUETO tablets contain the following non-medicinal ingredients: arginine, colloidal silicon dioxide, copovidone, magnesium stearate, maize starch. In addition, the film coating contains the following inactive ingredients: hypromellose, iron oxide red, iron oxide yellow, propylene glycol, talc, titanium dioxide.

What dosage forms it comes in:
JENTADUETO tablets contain linagliptin/metformin hydrochloride 2.5 mg/500 mg, 2.5 mg/850 mg, or 2.5 mg/1000 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Lactic acidosis is a rare but serious buildup of acid in the blood. It can cause death. It must be treated in the hospital. JENTADUETO contains a drug called metformin hydrochloride. If you build up too much metformin in your blood you are at risk for lactic acidosis.

Alcohol increases the risk of lactic acidosis caused by metformin. Do not "binge" drink or drink alcohol often when you are taking JENTADUETO.

Lactic Acidosis
Stop taking JENTADUETO if you get any of the following symptoms, which could be signs of lactic acidosis:
- feel very weak or tired;
- have unusual (not normal) muscle pain;
- have trouble breathing;
- have unusual sleepiness or sleep longer than usual;
- have sudden stomach or intestinal problems with nausea and vomiting or diarrhea;

- feel cold, especially in your arms and legs;
- feel dizzy or light-headed;
- have a slow or irregular heartbeat;
- your medical condition suddenly changes.

You have a higher chance of getting lactic acidosis if you:
- have severe kidney problems. Your kidneys can be affected by certain x-ray tests that use injected dye. JENTADUETO is usually stopped before and for two days after such a test. Your doctor should discuss this with you;
- have liver problems;
- have congestive heart failure that requires treatment with medicines;
- drink alcohol very often, or drink a lot of alcohol in short-term ("binge" drinking);
- get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids;
- have certain x-ray tests with dyes or contrast agents that are injected into your body;
- have surgery;
- have a heart attack, severe infection, or stroke;
- are 80 years of age or older and have not been assessed for kidney function;
- take other medications.

BEFORE or while taking JENTADUETO talk to your physician or pharmacist if you:
- are older than 65 years of age;
- take sulfonylurea or insulin. When JENTADUETO is used in combination with sulfonylurea or insulin, low blood sugar can occur. Your physician may consider lowering the dose of the sulfonylurea or insulin. Take precautions to avoid low blood sugar while driving or using machinery;
- have liver problems;
- have or have had pancreas problems, such as inflammation of the pancreas (pancreatitis);
- you have risk factors for pancreatitis such as:
  - gallstones (solid particles that form in the gall bladder),
  - a history of alcoholism,
  - high triglyceride levels;
- have any skin problems;
- you have heart problems including congestive heart failure (a condition where your heart becomes weaker and less able to pump the blood that your body needs);
- you have or have had severe kidney problems;
- had an organ transplant;
- have human immunodeficiency syndrome (HIV);
- have any other medical condition including: Vitamin B_{12} deficiency or anemia or hypothyroidism (low levels of thyroid hormones).

JENTADUETO is not recommended for children and adolescents under 18 years of age.

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

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

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

INTERACTIONS WITH THIS MEDICATION

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

This includes prescription and non-prescription drugs, vitamins, and herbal supplements. JENTADUETO may interact with other medications. This may cause serious side effects. This can be less control of your blood sugar or low blood sugar.

If you start any new medicine, tell your healthcare professional.

The following may interact with JENTADUETO:
- rifampin;
- other diabetes drugs such as glyburide;
- furosemide;
- nifedipine (used to treat high blood pressure and chest pain);
- certain "blood thinners" (phenprocoumon or other vitamin K anticoagulants);
- cationic drugs (e.g. amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin);
- Other drugs that tend to produce high blood sugar (hyperglycemia) and may lead to a loss of blood sugar control. Some example of drugs that can increase the blood sugar include:
  - thiazide and other diuretics (water pills);
  - corticosteroids (used to treat joint pain and swelling);
  - phenothiazines (antipsychotic medicine);
  - thyroid products;
  - estrogens or estrogens plus progestogen (female hormones);
  - oral contraceptives (birth control pills);
  - phenytoin (used to treat epilepsy);
  - nicotinic acid (used to prevent and treat niacin deficiency);
  - sympathomimetics (used for heart problems);
  - calcium channel blocking drugs (used for high blood pressure);
  - isoniazid (used to treat tuberculosis);
  - beta-2-agonists (used to treat breathing problems);
  - carbonic anhydrase inhibitors.
- ACE inhibitors drugs may lower blood glucose and the combination with JENTADUETO should be carefully monitored.

PROPER USE OF THIS MEDICATION

Your doctor will individualize your starting dose of JENTADUETO based on your current treatment regimen. Take JENTADUETO exactly as your physician has prescribed. Your physician will tell you how many JENTADUETO tablets to take and how often you should take them.

Your physician may adjust your dose, if needed to further control your blood sugar level.

Usual Adult Dose:
JENTADUETO should be given 2 times a day by mouth with meal to lower your chance of an upset stomach.

Continue to take JENTADUETO as long as your physician prescribes it so you can continue to help control your blood sugar.

You may need to stop JENTADUETO for a short time. Call your physician for instructions if you:
- have a condition that may be associated with dehydration (large loss of body fluids) such as being sick with severe vomiting, diarrhea or fever, or if you drink fluids a lot less than normal;
- plan to have surgery;
- are going to get or receive an injection of dye or contrast agent for an x-ray procedure.

Overdose:

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

Missed Dose:
If you forget to take a dose of JENTADUETO, take it as soon as you remember. If you do not remember until it is the time for your next dose, skip the missed dose and go back to your regular schedule. Do not take a double dose of JENTADUETO at the same time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

Side effects with JENTADUETO include:
- Cough
- Inflamed nose or throat (nasopharyngitis), sore throat, cold symptoms, stuffy or runny nose
- High blood lipase or amylase
- Hives or nettle rash (urticaria)
- Rash, itching
- Constipation
- Gastrointestinal symptoms: diarrhea, constipation, nausea, vomiting, abdominal bloating, upset stomach, gas and loss of appetite
- High blood triglyceride
- Mouth sores (mouth ulceration)

JENTADUETO can cause abnormal blood test results. Your physician will do blood tests before you start JENTADUETO and while you take it. They may check your blood sugar, liver and thyroid function, amount of vitamin B_{12} and how well your kidneys are working. Your doctor will decide when to perform blood tests and will interpret the results.

Your skin may be more sensitive to sunlight when you take JENTADUETO. Protect your skin from the sun.

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

Symptoms / Effects	Talk with your physician or pharmacist		Stop taking drug and call your physician or pharmacist
	Only if severe	In all cases	
Very Common			
Hypoglycemia (low blood sugar when used with a sulfonylurea or insulin): shaking, sweating, rapid heartbeat, hunger, headache, anxiety, change in vision, tingling lips, paleness, mood change, vagueness or confusion		✓	
Common			
Hypersensitivity (allergic reactions): rash, hives, and swelling of the face, lips, mouth, tongue or throat that may cause difficulty in breathing or swallowing and wheezing and shortness of breath			✓
Rare			
Lactic Acidosis (high level of lactic acid in the blood): malaise or feeling of general discomfort, feeling very weak or tired, low blood pressure, uneasiness or pain, unusual muscle pain, trouble breathing, unusual sleepiness or sleeping longer than usual, sudden stomach or intestinal problems with nausea and vomiting or diarrhea, feeling cold especially in your arms and legs, feeling dizzy or light-headed or suddenly developing a slow or irregular heartbeat			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptoms / Effects	**Talk with your physician or pharmacist**		**Stop taking drug and call your physician or pharmacist**
	Only if severe	**In all cases**	
Pancreatitis (inflammation of the pancreas): prolonged severe abdominal pain which may be accompanied by vomiting; pain may spread out towards the back			✓
Severe skin reactions including bullous pemphigoid: redness, peeling skin, and/or blistering of the skin, lips, eyes or mouth			✓
Hemolytic anemia (when red blood cells are destroyed faster than bone marrow can replace them): fatigue, pale colour, rapid heartbeat, shortness of breath, dark urine, chills, and backache			✓
Encephalopathy (disease of the brain that severely alters thinking): muscle weakness in one area, poor decision-making or concentration, involuntary twitching, trembling, difficulty speaking or swallowing, seizures			✓
Peripheral neuropathy (a result of damage to your peripheral nerves): gradual onset of numbness, prickling or tingling in your feet or hands, which can spread upward into your legs and arms, sharp, jabbing, throbbing, freezing or burning pain, extreme sensitivity to touch, lack of coordination and falling, muscle weakness or paralysis if motor nerves are affected			✓
Hypothyroidism (low levels of thyroid hormone): fatigue, feeling cold, dry skin, poor memory and concentration, weight gain		✓	
Very Rare			
Vitamin B_{12} deficiency (decreased vitamin B_{12} levels in the blood): fatigue, shortness of breath, tingling or numbness of the fingers or toes, difficulty walking properly, irritability, confusion, tender calves		✓	
Hepatitis (inflammation of the liver) or liver disorder: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		✓	
Rhabdomyolysis (breakdown of damaged muscle): muscle spasms, weakness, red-brown (tea-coloured) urine			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptoms / Effects	**Talk with your physician or pharmacist**		**Stop taking drug and call your physician or pharmacist**
	Only if severe	**In all cases**	
Unknown			
Arthralgia: severe joint pain		✓	

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

HOW TO STORE IT

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

Keep JENTADUETO and all medicines safely away from children.

Reporting Side Effects

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

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

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

MORE INFORMATION

If you want more information about JENTADUETO:

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

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

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