PRODUCT MONOGRAPH

Pr JENTADUETO®

Linagliptin/Metformin Hydrochloride Tablets

2.5 mg/500 mg, 2.5 mg/850 mg and 2.5 mg/1000 mg

Oral Antihyperglycemic Agent
DPP-4 Inhibitor
Incretin Enhancer

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Linagliptin/Metformin Hydrochloride Tablets

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) is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate, in patients inadequately controlled on metformin alone or in patients already being treated and well controlled with the free combination of linagliptin and metformin.

JENTADUETO is indicated in combination with a sulfonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus inadequately controlled on metformin and a sulfonylurea.

Geriatrics (≥ 65 years of age):
Linagliptin has been studied in a limited number of patients >75 years.
As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, JENTADUETO should be used with caution as age increases. Elderly patients taking JENTADUETO should have their renal function monitored regularly (see WARNINGS AND PRECAUTIONS, Special Populations, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

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

CONTRAINDICATIONS

- Unstable and/or insulin-dependent (Type 1) diabetes mellitus.
- Acute or chronic metabolic acidosis, diabetic ketoacidosis, with or without coma, history of ketoacidosis with or without coma. Diabetic ketoacidosis should be treated with insulin.
- In patients with a history of lactic acidosis, irrespective of precipitating factors.
- In the presence of renal impairment or when renal function is not known, and also in patients with serum creatinine levels above the upper limit of normal range. Renal disease or renal dysfunction, e.g., as suggested by serum creatinine levels ≥136 µmol/L [males], ≥ 124 µmol/L [females], or abnormal creatinine clearance (< 60 mL/min), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (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 generally be avoided 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.
- Known hypersensitivity to linagliptin, metformin or to any ingredient in the formulation (see WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions and ADVERSE REACTIONS, Post-Marketing Adverse Drug Reactions). For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- During pregnancy and breastfeeding.

JENTADUETO should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because the use of such products may result in acute alteration of renal function (see WARNINGS AND PRECAUTIONS, Radiologic studies).

JENTADUETO should be temporarily discontinued for any surgical procedure necessitating restricted intake of food and fluids and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- 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 Endocrine and Metabolism, Lactic Acidosis section below).

- 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 Endocrine and Metabolism, Lactic Acidosis section below).

General

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

The use of JENTADUETO in combination with insulin is not indicated due to an increase in cardiovascular risk which cannot be excluded (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, Cardiovascular).

Patient Selection and Follow-up

Careful selection of patients is important. It is imperative that there be rigid attention to diet and careful adjustment of dosage. Regular thorough follow-up examinations are necessary.

If vomiting occurs, withdraw drug temporarily, exclude lactic acidosis, then resume dosage cautiously (see ADVERSE REACTIONS).

Particular attention should be paid to short range and long range complications which are peculiar to diabetes. Periodic cardiovascular, ophthalmic, hematological, hepatic and renal assessments are advisable.

Use of JENTADUETO must be considered as treatment in addition to proper dietary regimen and not as a substitute for diet.

Care should be taken to ensure that JENTADUETO is not given when a contraindication exists.

If during JENTADUETO therapy the patient develops acute inter-current disease such as: clinically significant hepatic dysfunction, cardiovascular collapse, congestive heart failure, acute myocardial infarction, or other conditions complicated by hypoxemia, the drug should be discontinued.

Cardiovascular

Linagliptin

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

Patients using insulin: JENTADUETO is not indicated in combination with insulin due to an increase in cardiovascular risk, which cannot be excluded. In a Phase III randomized, double-blind, placebo-controlled, parallel group efficacy and safety study of linagliptin 5mg (with or without metformin), administered orally once daily for at least 52 weeks in 1255 type 2 diabetic patients in combination with basal insulin therapy, a composite endpoint of cardiovascular and cerebrovascular death, myocardial infarction, and stroke occurred in 0.80% (5 of 627) of patients in the placebo group and 1.59% (10 of 628) of patients in the linagliptin group (Hazard Ratio 1.93 [0.66, 5.66]). The incidence of cardiovascular death was 0.16 %(1 of 627) in the placebo group and 0.80% (5 of 628) in the linagliptin group (Hazard ratio 4.79 [0.56, 40.98]). These findings were not statistically significant.

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

Metformin

Driving and Operating Machinery

Patients should be warned about driving a vehicle or operating machinery under conditions where risks of hypoglycemia are present **(**see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypoglycemia).

Hypoxic States: Cardiovascular collapse (shock) from whatever cause, 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. When such events occur in patients on JENTADUETO therapy, the drug should be promptly discontinued.

Endocrine and Metabolism

Lactic Acidosis: 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. 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. 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, metformin 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 metformin, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin 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. Metformin 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 metformin, 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. Such management often results in prompt reversal of symptoms and recovery (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.

Hypoglycemia:

Use with Sulfonylreas: When JENTADUETO was 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, DRUG INTERACTIONS, Overview, CLINICAL TRIAL Adverse Drug Reactions and DOSAGE AND ADMINISTRATION). Therefore, caution is advised when JENTADUETO is used in combination with a sulfonylurea. A dose reduction of the sulfonylurea may be considered to reduce the risk of hypoglycemia.

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 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 induces a reduction in thyrotropin (thyroid stimulating hormone (TSH)) levels in patients with treated or untreated hypothyroidism (see ADVERSE REACTIONS, Post-Market Adverse Drug 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, Levothyroxine).

Change in clinical status of previously controlled diabetes patients: 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: When a patient stabilized on JENTADUETO is exposed to stress such as fever, trauma, infection, or surgery, a loss of control of blood glucose may occur. At such times, it may be necessary to temporarily discontinue JENTADUETO and administer insulin.

Use with P-gp/CYP3A4 inducers: Long term co-treatment with strong inducers of P-gp or CYP3A4 (e.g. rifampicin) may reduce the glycemic lowering effect of JENTADUETO. Where efficacy is insufficient, the physician should consider either a change of the P-gp/CYP3A4 inducer to a non P-gp/CYP3A4 inducing compound or a change of JENTADUETO to another oral antidiabetic (see DRUG INTERACTIONS).

Vitamin B_{12} levels: 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 B12 levels which may cause peripheral neuropathy. Serious cases of peripheral neuropathy have been reported with metformin treatment in the context of vitamin B12 deficiency (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions). Monitoring of serum vitamin B12 levels is recommended (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Hematologic:
Serious cases of metformin-induced hemolytic anemia, some with a fatal outcome, have been reported (see ADVERSE REACTIONS, Post-Market Adverse Drug 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

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

Metformin

Since impaired hepatic function has been associated with some cases of lactic acidosis, JENTADUETO should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Metformin is contraindicated in patients suffering from severe hepatic dysfunction (see CONTRAINDICATIONS).

Serious cases of pancreatitis have been reported in patients receiving metformin (see ADVERSE REACTIONS, Post-Market Adverse Drug 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.

Neurologic

Metformin

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

Pancreatic

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

Hypersensitivity Reactions

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

There have also been post-marketing reports of exfoliative skin conditions, including Stevens-Johnson syndrome, with other members of this class. Onset of these reactions occurred within the first 3 months after initiation of treatment, with some reports occurring after the first dose.

Immune

Immunocompromised patients: A dose-related mean decrease in absolute lymphocyte count was observed with other members of this class. When clinically indicated, such as in settings of unusual or prolonged infection, lymphocyte count should be measured. The effect of 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.

Peri-Operative Consideration

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 normal.

Radiological studies

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 in whom any such study is planned, JENTADUETO should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Renal

Linagliptin

Clinical study experience with linagliptin in patients with End Stage Renal Disease (ESRD) and those on dialysis is limited.

Metformin

Metformin hydrochloride is excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of the normal range for their age should not receive JENTADUETO. As metformin is not used in patients with creatinine clearance < 60 mL/min, JENTADUETO is contraindicated in patients with abnormal creatinine clearance (< 60 mL/min). Serum creatinine levels should be determined before initiating treatment and regularly thereafter:

- at least annually in patients with normal renal function,
- at least two to four times a year in patients with serum creatinine levels at the upper limit of normal and in elderly subjects.

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. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy, or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug.

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.

Skin

Bullous pemphigoid
Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with the use of linagliptin and other DPP-4 inhibitors. 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.

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

Special Populations

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

Pregnant Women: JENTADUETO is contraindicated for use in pregnancy. 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.

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

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

Geriatrics (≥ 65 years of age):

Linagliptin

Linagliptin has been studied in limited number of patients >75 years. Although linagliptin is minimally excreted by the kidney; greater sensitivity of some older individuals cannot be ruled out.

Metformin

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients. Metformin is substantially excreted by the kidney. Considering that 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 (CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, Renal and CLINICAL PHARMACOLOGY). The risk of serious adverse reactions to the drug is greater in patients with impaired renal function, metformin should only be used in patients with normal renal function (see CONTRAINDICATIONS).

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

Monitoring of glycemic parameters: Response to all diabetic therapies should be monitored, by periodic measurements of blood glucose and HbA1c levels, with a goal of decreasing these levels towards the normal range. HbA1c is especially useful for evaluating long-term glycemic control. Periodic monitoring of blood and/or urinary glucose is necessary to detect primary and secondary failure (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Loss of control of blood glucose).

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, Cationic Drugs and Other).

When linagliptin is co-administered with strong inducers of P-gp or CYP3A4, the physician should monitor glucose more closely. In cases of insufficient efficacy, the physician should consider either a change of the P-gp/CYP3A4 inducer to a non P-gp/CYP3A4 inducing compound or a change of JENTADUETO to another oral antidiabetic (see DRUG INTERACTIONS).

Monitoring of hematologic parameters: 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.

Impairment of vitamin B12 absorption has been reported in some patients, and long-term treatment with metformin has been associated with reductions in vitamin B12 serum levels. Periodic measurements of serum vitamin B12 levels should be performed in patients on long-term treatment with metformin, especially in patients with anemia or neuropathy (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism**,** Vitamin B12 levels).

Regular monitoring of thyroid-stimulating hormone (TSH) levels is recommended in patients with hypothyroidism (see WARNINGS AND PRECAUTIONS, Hypothyroidism and ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

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, Hypothyroidism and DRUG INTERACTIONS, Levothyroxine).

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, Other).

Monitoring of renal function: Metformin is known to be substantially excreted by the kidneys. The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive JENTADUETO. In patients with advanced age, JENTADUETO should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging can be associated with reduced renal function. In elderly patients, particularly those ≥80 years of age, renal function should be monitored regularly.

Before initiation of therapy with JENTADUETO and every 6 months thereafter, renal function should be assessed and verified as normal. 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.

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 hypoglycemias episodes were classified as severe.

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% placebo). The most frequently reported adverse event was hypoglycemia observed under the triple combination, linagliptin plus metformin plus sulfonylurea 22.9% vs. 14.8% in placebo. (See WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypoglycemia). In the pooled placebo controlled trials, nasopharyngitis was observed more frequently with linagliptin compared to placebo (5.9% vs. 4.7% placebo).

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

The main causes for discontinuation for linagliptin were diarrhea (0.2% vs. 0.1% placebo), glomerular filtration rate decreased (0.3% vs. 0.2% placebo), hyperglycemia (0.2% vs. 0.8% placebo) and hypoglycemia (0.2% vs. 0.0% placebo).

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

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

Metformin

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 Sections).

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 HCl) 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: 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. However, only five cases of megaloblastic anemia have been reported with metformin administration (none during U.S. clinical studies) 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 B12 deficiency (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Vitamin B12 levels).

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 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 adverse events, 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 4.

Combination therapy: linagliptin add-on to metformin

Table 2 Linagliptin in combination with metformin (pivotal trial 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	Pbo N (%)	Linagliptin N (%)
Number of patients	177 (100.0)	523 (100.0)
Infections and infestations	38 (21.5)	112 (21.4)
Nasopharyngitis	9 (5.1)	27 (5.2)
Influenza	5 (2.8)	18 (3.4)
Upper respiratory tract infection	4 (2.3)	15 (2.9)
Gastrointestinal disorders	20 (11.3)	58 (11.1)
Diarrhoea	4 (2.3)	15 (2.9)
Musculoskeletal and connective tissue disorders	14 (7.9)	58 (11.1)
Arthralgia	3 (1.7)	11 (2.1)
Respiratory, thoracic and mediastinal disorders	5 (2.8)	25 (4.8)
Cough	3 (1.7)	11 (2.1)

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

Table 3 Linagliptin in combination with metformin and sulfonylurea (pivotal trial 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	Pbo N (%)	Linagliptin N (%)
Number of patients	263 (100.0)	791 (100.0)
General disorders and administration site conditions	18 (6.8)	61 (7.7)
Asthenia	5 (1.9)	19 (2.4)
Infections and infestations	76 (28.9)	169 (21.4)
Nasopharyngitis	12 (4.6)	40 (5.1)
Metabolism and nutrition disorders	68 (25.9)	246 (31.1)
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)
Anaemia	25 (3.2)	17 (2.2)
Psychiatric disorders	68 (8.8)	61 (7.9)
Depression	24 (3.1)	22 (2.8)
Nervous system disorders	149 (19.2)	181 (23.4)
Headache	50 (6.4)	40 (5.2)
Vascular disorders	89 (11.5)	110 (14.2)
Arteriosclerosis	20 (2.6)	11 (1.4)
Respiratory, thoracic and mediastinal disorders	108 (13.9)	102 (13.2)
Cough	47 (6.1)	28 (4.9)
Gastrointestinal disorders	215 (27.7)	220 (28.4)
Constipation	33 (4.3)	16 (2.1)
Dyspepsia	23 (3.0)	17 (2.2)
Abdominal pain upper	18 (2.3)	17 (2.2)
Vomiting	17 (2.2)	12 (1.5)
Skin and subcutaneous tissue disorders	119 (15.3)	95 (12.3)
Eczema	18 (2.3)	15 (1.9)
Musculoskeletal and connective tissue disorders	257 (33.1)	244 (31.5)
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)

In a 24-week clinical study, a higher risk of increased serum lipase was observed for patients treated with linagliptin compared to placebo (see Abnormal Hematologic and Clinical Chemistry Findings).

Less Common Clinical Trial Adverse Drug Reactions (as investigator assessed) ≥0.1% and <2% (Drug-Related and Greater than Placebo in Pooled Placebo-Controlled Studies)

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

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 group) were:

- 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 time upper limit of normal, during treatment or post-treatment period (approximately 4 weeks); the upper limit of normal for lipase level in blood was 60 U/L);
- increases in uric acid (1.3% in the placebo group, 2.7 % in the linagliptin group; based on pooled placebo controlled trials).

Metformin

In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. 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 (see WARNINGS AND PRECAUTIONS).

Post-Marketing Adverse Drug Reactions

Linagliptin

Additional adverse reactions have been identified during post-marketing use of linagliptin, one of the components of JENTADUETO. These reactions have been reported when linagliptin has been used alone and/or in combination with other antihyperglycemic agents. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hepatic/biliary/pancreatic: pancreatitis
Immune system disorders: angioedema, urticaria, hypersensitivity, mouth ulceration
Musculoskeletal and connective tissue disorders: arthralgia
Skin and subcutaneous tissue disorders: rash, bullous pemphigoid

Metformin

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

Gastrointestinal Disorders: Abdominal discomfort, abdominal distension, abdominal pain, abdominal pain upper, 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, pancreatitis (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Investigations: Blood lactic acid increased.
Reduction of thyrotropin level in patients with treated or untreated hypothyroidism (see WARNINGS AND PRECAUTIONS, Hypothyroidism and Monitoring and Laboratory Tests).

Nervous System Disorders: Encephalopathy (see WARNINGS AND PRECAUTIONS, Neurologic).

Metabolism and Nutrition Disorders: Lactic acidosis, decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin, weight decreased, decreased appetite.

Peripheral neuropathy in patients with vitamin B12 deficiency (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Vitamin B12 levels).

Hypomagnesemia in the context of diarrhea.

Skin and Subcutaneous Tissue Disorders: Photosensitivity, erythema, pruritus, rash, skin lesion, and urticaria.

DRUG INTERACTIONS

Overview

Linagliptin and Metformin
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.

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

Linagliptin

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

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

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

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

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

Metformin

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

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

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

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

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

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

Metformin

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, Monitoring and Laboratory Tests), and metformin dosage adjusted as necessary (see DOSAGE AND ADMINISTRATION, Dosing Considerations).

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, Monitoring and Laboratory Tests)

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

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

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

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

Drug-Laboratory Interactions
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, Radiological Studies).

Drug-Lifestyle Interactions

Metformin

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).

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 dose of 2.5 mg linagliptin/1000 mg metformin hydrochloride twice daily.

JENTADUETO should be given twice daily with meals with gradual dose escalation to reduce the gastrointestinal undesirable effects associated with metformin.

In patients in whom the maximum dose fails to lower the blood glucose adequately, therapeutic alternatives should be considered.

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).

Renal Impairment
JENTADUETO is contraindicated in patients with renal insufficiency (creatinine clearance < 60 ml/min) due to the metformin component (see CONTRAINDICATIONS).

Hepatic Impairment
Use of JENTADUETO in patients with severe hepatic insufficiency is contraindicated. Since impaired hepatic function has been associated with some cases of lactic acidosis, JENTADUETO is not recommended in patients with clinical or laboratory evidence of hepatic disease (see CONTRAINDICATIONS).

Geriatrics (≥ 65 years of age):
As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, JENTADUETO should be used with caution as age increases. Elderly patients taking

JENTADUETO should have their renal function assessed prior to initiation of therapy with JENTADUETO and monitored regularly thereafter (see WARNINGS and PRECAUTIONS).

Pediatrics (< 18 years of age):
Safety and effectiveness of JENTADUETO in pediatric patients have not been studied. 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

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

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

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

Metformin

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,

Endocrine and Metabolism – Lactic Acidosis). 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, Hepatic/Biliary/Pancreatic).

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

Metformin is an antihyperglycemic agent, which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin is a biguanide derivative producing an antihyperglycemic effect which is observed in diabetic patients or in diabetic animals. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin may decrease hepatic glucose production, decrease intestinal absorption of glucose, and improve insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances, see

WARNINGS AND PRECAUTIONS, Hypoglycemia) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

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.

Metformin

Metformin hydrochloride may act via 3 mechanisms:
(1) reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis, (2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation, (3) and delay of intestinal glucose absorption. Metformin hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase.

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

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

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

Pharmacokinetics

The 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-Drug Interactions).

Metformin

The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin hydrochloride 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

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 n M) 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

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

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-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

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

Excretion:

Linagliptin

Following 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

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

Special Populations and Conditions

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

Geriatric (≥ 65 years of age):

Linagliptin

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

Metformin

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

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, Lactic Acidosis).

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

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 dose 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

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

Body Mass Index (BMI):

Linagliptin

No dose adjustment is required based on BMI.

Renal Impairment:

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 End Stage Renal Disease (n=6). The studies included patients with renal impairment classified on the basis of creatinine clearance as mild (50 to 80 mL/min), moderate (30 to 50 mL/min), and severe (<30 mL/min), as well as patients with End Stage Renal Disease (ESRD) on hemodialysis. In addition, patients with T2DM and severe renal impairment (n=10) were compared to T2DM patients with normal renal function (n=11) in a multiple-dose study.

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

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

After a single oral dose of linagliptin, exposure was 1.2- to 1.6-fold higher for patients with renal impairment (with or without T2DM) than for subjects with normal renal function (with or without T2DM).

Under steady-state conditions, (oral administration of multiple 5 mg doses), pharmacokinetic characteristics in patients with mild renal impairment were comparable to those of subjects with normal renal function. An overall increase in $AUC_{\tau,ss}$ 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. Use in these patients should be with caution.

Metformin

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

JENTADUETO is contraindicated in patients with renal insufficiency (creatine clearance < 60 mL/min) due to the metformin component (see CONTRAINDICATIONS).

Hepatic Impairment:

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

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

Use of JENTADUETO in patients with severe hepatic insufficiency is contraindicated. JENTADUETO is not recommended in patients with clinical or laboratory evidence of hepatic disease (see CONTRAINDICATIONS).

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.

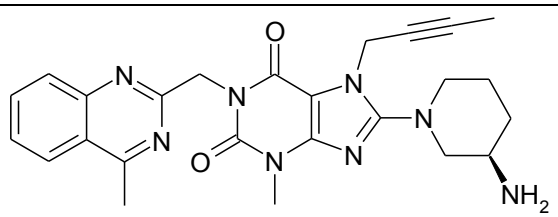
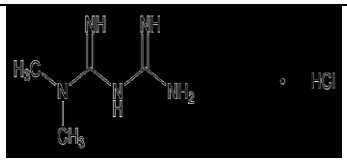
JENTADUETO tablets 2.5 mg/1000 mg, are light pink, oval biconvex film-coated tablets containing, 2.5 mg of linagliptin and 1000 mg of metformin hydrochloride. JENTADUETO tablets are debossed with "D2/1000" on one side and the Boehringer Ingelheim logo on the other side. They are supplied as blisters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

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 5 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, randomised, double-blind, placebo-controlled	linagliptin 5 mg or placebo Oral, 24 weeks	Total: 701 Linagliptin : 524 Placebo: 177	56 (21-79)	46/54
1218.46	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, randomised, 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, randomised, double-blind, active-controlled	linagliptin 5 mg or glimepiride (forced titration from 1 mg to max. 4 mg) Oral, 52 weeks	Total: 1560 Linagliptin : 779 Glimepiride: 781	60 (28-80)	40/60
Add on Combination Therapy with Metformin and a Sulfonylurea					
1218.18	Multicentre, randomised, double-blind, placebo-controlled	linagliptin 5 mg or placebo Oral, 24 weeks	Total: 1058 Linagliptin: 793 Placebo: 265	58 (23-79)	53/47

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 6). Body weight did not differ significantly between the groups.

Table 6: Glycemic Parameters at Final Visit (Placebo-Controlled Study) for TRAJENTA® in Combination with Metformin (BI study 1218.17)

	TRAJENTA® 5 mg + Metformin	**Placebo + Metformin**
HbA_{1C} (%)	**n = 513**	**n =175**
Baseline (mean)	8.09	8.02
Change from baseline (adjusted mean)	-0.49	0.15
Difference from placebo + metformin (adjusted mean) (95% CI)	-0.64 (-0.78, -0.50)	
Patients (%) achieving HbA_{1C} <7%	145 (28.3)	20 (11.4)
FPG (mmol/L)	**n = 495**	**n = 159**
Baseline (mean)	9.39	9.10
Change from baseline (adjusted mean)	-0.59	0.58
Difference from placebo + metformin (adjusted mean) (95% CI)	-1.17 (-1.52, -0.83)	
2-hour PPG (mmol/L)	**n = 78**	**n = 21**
Baseline (mean)	15.0	15.22
Change from baseline (adjusted mean)	-2. 71	1.01
Difference from placebo + metformin (adjusted mean) (95% CI)	-3.72 (-5.26, -2.20)	

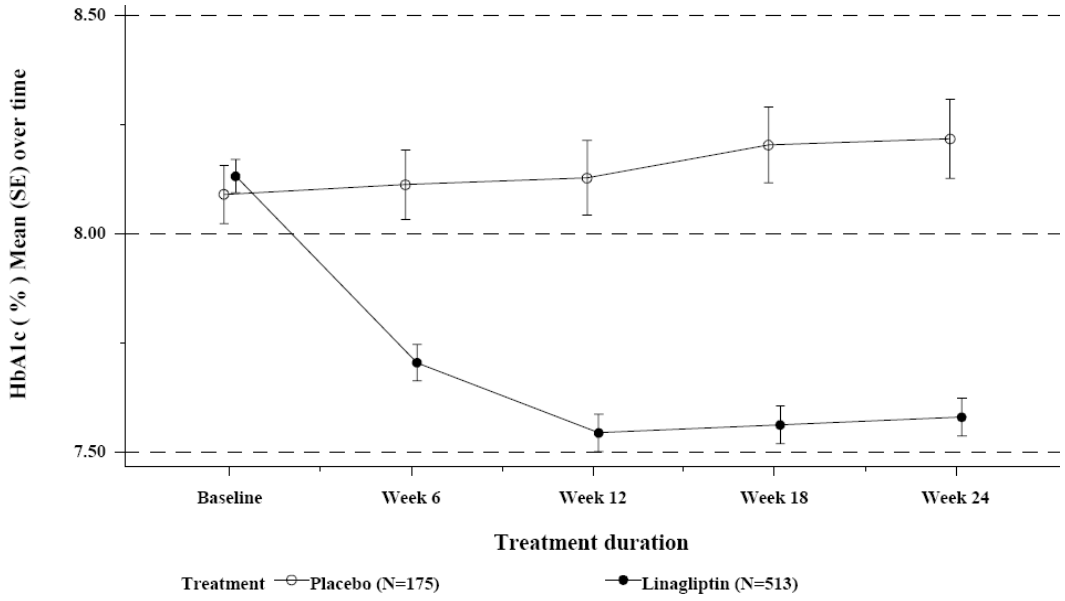


Figure 1 Mean HbA_{1C} (%) over 24 Weeks with TRAJENTA®/ Metformin and Placebo/ Metformin in Patients with Type 2 Diabetes (BI study 1218.17, add on to metformin patients)

BI Study 1218.46

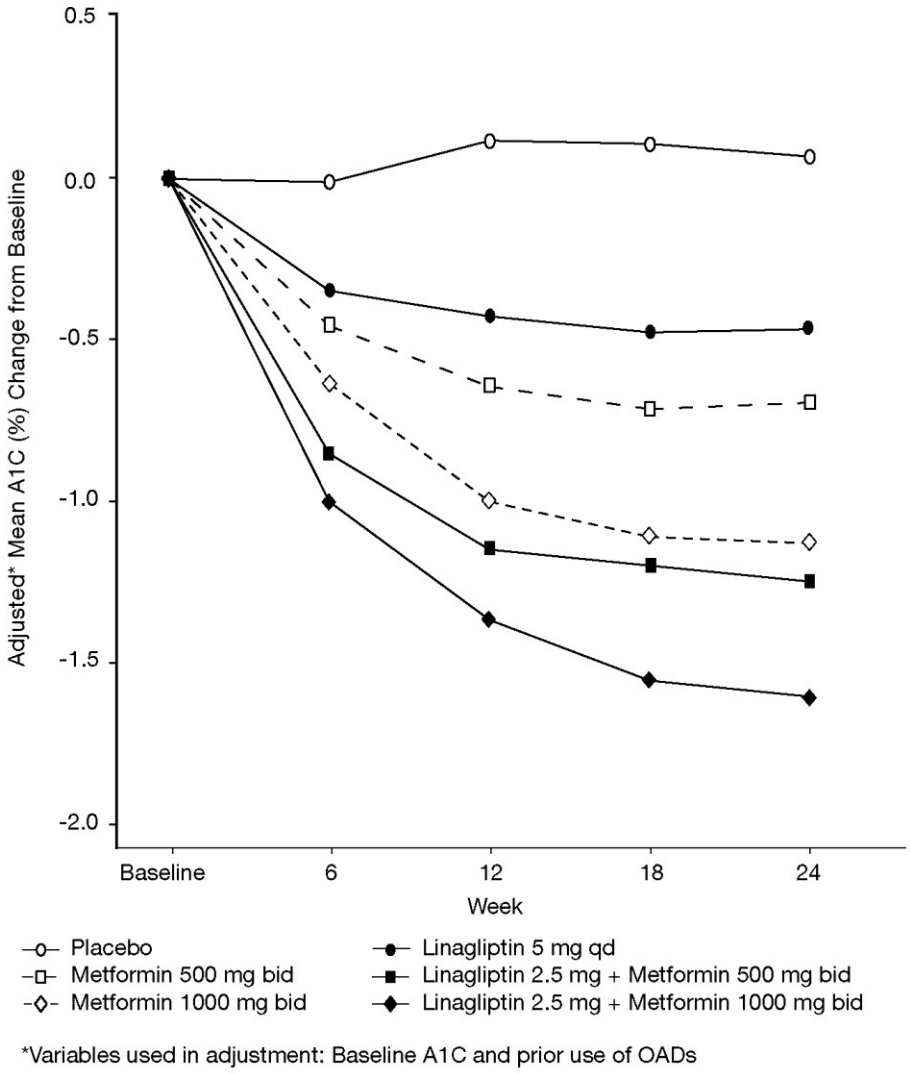
In a 24-week placebo-controlled factorial study, linagliptin 2.5 mg twice daily in combination with metformin (500 mg or 1000 mg twice daily) provided significant improvements in glycemic parameters compared with either monotherapy as summarized in Table 7 (mean baseline HbA1c 8.65%) and Figure 2.

Table 7: 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**
HbA1c (%)						
Number of patients	n = 65	n = 135	n = 141	n = 137	n = 138	n = 140
Baseline (mean)	8.7	8.7	8.7	8.7	8.5	8.7
Change from baseline (adjusted mean)	0.1	-0.5	-0.6	-1.2	-1.1	-1.6
Difference from placebo (adjusted mean) (95% CI)	--	-0.6 (-0.9, -0.3)	-0.8 (-1.0, -0.5)	-1.3 (-1.6, -1.1)	-1.2 (-1.5, 0.9)	-1.7 (-2.0, -1.4)
Patients (n, %) achieving HbA1c <7%	7 (10.8)	14 (10.4)	27 (19.1)	42 (30.7)	43 (31.2)	76 (54.3)
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 A1C (%) over 24 Weeks with Linagliptin and Metformin, Alone and in Combination in Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Diet and Exercise - FAS completers (LOCF).



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

Mean reductions from baseline in HbA1c were generally greater for patients with higher baseline HbA1c 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 2.5mg 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 HbA1c reductions of -0.80 % (from baseline 7.98%), and -0.74% (from baseline 7.96%) compared to placebo (Table 8).

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 8: 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	**Lina 2.5mg bid + Metformin**	**Lina 5mg 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 9). Body weight did not differ significantly between the groups.

Table 9 Glycemic Parameters at Final Visit (24-Week Study) for TRAJENTA® in Combination with Metformin and Sulfonylurea (BI Study 1218.18)

	TRAJENTA® 5 mg + Metformin + SU	**Placebo + Metformin + SU**
HbA_{1C} (%)	**n = 778**	**n = 262**
Baseline (mean)	8.15	8.14
Change from baseline (adjusted mean)	-0.72	-0.10
Difference from placebo (adjusted mean) (95% CI)	-0.62 (-0.73, -0.50)	
Patients n (%) achieving A1C <7%	243 (31.2)	24 (9.2)
FPG (mmol/L)	**n = 739**	**n = 248**
Baseline (mean)	8.84	9.03
Change from baseline (adjusted mean)	-0.26	0.45
Difference from placebo (adjusted mean) (95% CI)	-0.71 (-1.0, -0.40)	

SU = sulfonylurea

Linagliptin 24 month data, as add on to metformin in comparison with glimepride (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%.

Cardiovascular risk

In a prospective meta-analysis of independently adjudicated cardiovascular events from19 phase III clinical studies of 12-104 weeks duration (18 placebo-controlled trials of at least 12 weeks in duration, 1 glimepiride-controlled trial of 104 weeks in duration) involving 9297 patients with type 2 diabetes (2675 on placebo, 5847 on linagliptin, 775 on glimepiride), linagliptin treatment was not associated with an increase in cardiovascular risk. A composite endpoint-consisting of: the occurrence or time to first occurrence of CV death, non-fatal myocardial infarction, and non-fatal stroke, was non-significantly lower for linagliptin versus combined active and placebo comparators [Hazard ratio 0.74 (95% confidence interval 0.49, 1.14)]. Comparisons of linagliptin with placebo only were not statistically significant [Hazard ratio 1.10 (95% confidence interval 0.61; 2.01)], whereas comparisons of linagliptin with glimepiride were statistically significant (Hazard ratio 0.47; 95% confidence interval 0.23; 0.97).

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

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

Endpoint	Hazard Ratios (95% Confidence Intervals)		
	Linagliptin (N=5847) vs. Combined Placebo + Glimepiride (N=3450)	Linagliptin (N=5071) vs. Placebo (N=2675)	Linagliptin (N=776) vs. Glimepiride (N=775)
Expanded MACE: • CV death • non-fatal myocardial infarction • non-fatal stroke • hospitalization due to unstable angina	0.78 (0.55, 1.12)	1.09 (0.68, 1.75)	0.45 (0.23, 0.90)
Core MACE: • CV death • non-fatal myocardial infarction • non-fatal stroke	0.74 (0.49, 1.14)	1.10 (0.61, 2.01)	0.47 (0.23, 0.97)

Comparative Bioavailability Studies

In a bioequivalence study of JENTADUETO 2.5mg/500mg (linagliptin/metformin HCl), both the linagliptin component and the metformin component were bioequivalent to 2.5 mg linagliptin and 500 mg metformin HCl (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 HCl) are proportionally formulated; demonstration of bioequivalence of JENTADUETO (2.5/500) 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 10.

Table 10 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) 2.5/500 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 2.5/1000 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.

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

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

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

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

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 along with diet and exercise to improve control of blood sugar in adults with type 2 diabetes:
- in patients who are not controlled on metformin alone;
- in patients currently on linagliptin (TRAJENTA) and metformin alone; OR
- in combination with a sulfonylurea, in patients who are not controlled on metformin and a sulfonylurea.

What it does:
JENTADUETO is a prescription medicine that contains 2 diabetes medicines, linagliptin and metformin.

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:
You should not take JENTADUETO if you:
- are allergic (hypersensitive) to linagliptin, metformin or any of the non-medicinal ingredients in JENTADUETO;
- 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 or diabetic ketoacidosis (increased ketones in the blood or urine);
- have certain x-ray tests with dyes or contrast agents that are injected into your body;
- are stressed, have severe infections, are experiencing trauma, prior to surgery or during the recovery phase;
- have cardiovascular collapse (abrupt failure of blood circulation) or cardiorespiratory insufficiency;
- 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 breast-feeding (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 is supplied as tablets containing 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
JENTADUETO contains metformin which can rarely cause lactic acidosis. Lactic acidosis can cause death and must be treated in the hospital (see section Lactic Acidosis below). Therefore, you should not drink a lot of alcohol if you take JENTADUETO (see section Lactic Acidosis below).

Lactic Acidosis

Stop taking JENTADUETO and call your doctor right away 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.

You have a higher chance of getting lactic acidosis if you:
- have kidney problems. People whose kidneys are not working properly should not take JENTADUETO;
- 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;
- have metabolic acidosis or diabetic ketoacidosis (increased ketones in the blood or urine).

BEFORE you use JENTADUETO talk to your doctor or pharmacist if you:

- are taking insulin because JENTADUETO is not approved for use with insulin;
- have kidney problems;
- have an injection of dye or contrast agents for an x-ray procedure;
- have liver problems;
- have pancreas problems, such as inflammation of the pancreas;
- have any skin problems;
- have had allergic reaction to any other medicines that you take to control the blood sugar;
- have heart problems, including congestive heart failure;
- drink alcohol very often, or drink a lot of alcohol in short term ("binge" drinking);
- are pregnant or planning to become pregnant;
- are breast-feeding or plan to breast-feed;
- have any other medical condition including: Vitamin B-12 deficiency or anemia or hypothyroidism (low levels of thyroid hormones).

Do not drive or operate machines if you develop hypoglycemia (low blood sugar).

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all the drugs you take. This includes prescription and non-prescription drugs, vitamins, and herbal supplements. JENTADUETO may interact with other medications. This may cause serious side effects.

Know the medicines you take. Keep a list of your drugs and show it to your doctor and/or pharmacist each time you get a new drug.

Discuss with your doctor or pharmacist if you take any of the following:

- rifampin;
- other diabetes drugs such as glyburide;
- furosemide (diuretic (water pills), used for oedema (fluid retention), and high blood pressure);
- nifedipine (calcium-channel blocker used for high blood pressure; angina; Raynaud's phenomenon);
- certain "blood thinners" (phenprocoumon or other vitamin K anticoagulants);
- cationic drugs (e.g. amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin);
- drugs that can increase the blood sugar include:
  - thiazide and other diuretics (water pills);
  - corticosteroids (e.g. prednisone);
  - phenothiazines (antipsychotic medicine);
  - thyroid hormone replacement drugs e.g. levothyroxine;
  - estrogens or estrogens plus progestogen (female hormones);
  - oral contraceptives (birth control pills);
  - phenytoin (medicine used to treat epilepsy);
  - nicotinic acid (medicine used to prevent and treat niacin deficiency);
  - sympathomimetics;
  - calcium channel blocking drugs (such as nifedipine, amlodipine, felodipine, verapamil, diltiazem);
  - isoniazid (medicine used to treat active tuberculosis infections);
  - medicine for asthma such as salbutamol or formoterol (beta-2-agonists);
- ACE inhibitors (drugs used to treat hypertension (high blood pressure)) may lower blood glucose and the combination with JENTADUETO should be carefully monitored.

PROPER USE OF THIS MEDICATION

Usual Adult Dose:
2.5/500 mg, or 2.5/850 mg, or 2.5/1000 mg twice daily taken with meals. Take JENTADUETO tablet with meals to lower the chance of having an upset stomach.

Overdose:
In general, an overdose may lead to increased symptoms including stomach ache, nausea, vomiting, diarrhea, drowsiness, weakness, dizziness, malaise, and headache.
A serious, life-threatening condition called lactic acidosis may also occur (see **WARNINGS and PRECAUTIONS, Lactic Acidosis**).

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. However, if it is nearly time for the next dose, skip the missed dose.
- Do not take a double dose to make up for a forgotten dose. Never take two doses of JENTADUETO at the same time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

- Stuffy nose or runny nose and sore throat (nasopharyngitis);
- Diarrhea, nausea, and stomach upset, bloating, flatulence;
- Mouth ulceration;
- Low blood sugar (hypoglycemia): If you take JENTADUETO with another medication that can cause low blood sugar, such as sulfonylureas, you have a higher risk of having low blood sugar. If you have symptoms of low blood sugar, you should check your blood sugar and treat it, then call your doctor.

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

JENTADUETO can cause abnormal blood test results. 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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Common	**Hypoglycemia** (low blood sugar): shaking; sweating, feeling very anxious, or confused; fast heartbeat; feeling excessive hunger; headache; change in vision		✓	✓
Uncommon	**Allergic reactions**: hives; swelling of the face, lips, mouth, tongue or throat; difficulty breathing or swallowing; wheezing; shortness of breath		✓	✓
Rare	**Lactic Acidosis** (high level of lactic acid in the blood): feeling very weak or tired, 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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor 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: rashes, 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			✓
Unknown	**Arthralgia**: severe joint pain		✓	

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

HOW TO STORE IT

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

Keep out of reach and sight of 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.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://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html), 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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