

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use JENTADUETO XR safely and effectively. See full prescribing information for JENTADUETO XR.

JENTADUETO® XR (linagliptin and metformin hydrochloride extended-release) tablets, for oral use
Initial U.S. Approval: 2012

WARNING: LACTIC ACIDOSIS

See full prescribing information for complete boxed warning.

- Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL. (5.1)
- Risk factors include renal impairment, concomitant use of certain drugs, age ≥ 65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the Full Prescribing Information. (5.1)
- If lactic acidosis is suspected, discontinue JENTADUETO XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)

INDICATIONS AND USAGE

JENTADUETO XR is a dipeptidyl peptidase-4 (DPP-4) inhibitor and biguanide combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate (1.1)

Important limitations of use:

- Not for treatment of type 1 diabetes or diabetic ketoacidosis (1.2)
- Has not been studied in patients with a history of pancreatitis (1.2)

DOSAGE AND ADMINISTRATION

- Individualize the starting dose of JENTADUETO XR based on the patient's current regimen (2.1)
- Do not exceed a total daily dose of linagliptin 5 mg and metformin 2000 mg (2.1)
- Give once daily with a meal (2.1)
- Swallow whole; do not split, crush, dissolve, or chew (2.1)
- Prior to initiation, assess renal function with estimated glomerular filtration rate (eGFR) (2.2)
 - Do not use in patients with eGFR below 30 mL/min/1.73 m²
 - Initiation is not recommended in patients with eGFR between 30 - 45 mL/min/1.73 m²
 - Assess risk/benefit of continuing if eGFR falls below 45 mL/min/1.73 m²
 - Discontinue if eGFR falls below 30 mL/min/1.73 m²
- JENTADUETO XR may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets:

5 mg linagliptin/1000 mg metformin hydrochloride extended-release
2.5 mg linagliptin/1000 mg metformin hydrochloride extended-release (3)

CONTRAINDICATIONS

- Severe renal impairment (eGFR below 30 mL/min/1.73 m²) (4)
- Metabolic acidosis, including diabetic ketoacidosis (4)
- History of hypersensitivity reaction to linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity (4)
- Hypersensitivity to metformin (4)

WARNINGS AND PRECAUTIONS

- Lactic acidosis: See boxed warning (5.1)
- There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis. If pancreatitis is suspected, promptly discontinue JENTADUETO XR. (5.2)
- Heart Failure: Heart failure has been observed with two other members of the DPP-4 inhibitor class. Consider risks and benefits of JENTADUETO XR in patients who have known risk factors for heart failure. Monitor for signs and symptoms. (5.3)
- Hypoglycemia: When used with an insulin secretagogue (e.g., sulfonylurea (SU)) or insulin, consider lowering the dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia (5.4)
- Hypersensitivity reactions: There have been postmarketing reports of serious hypersensitivity reactions in patients treated with linagliptin (one of the components of JENTADUETO XR) including anaphylaxis, angioedema, and exfoliative skin conditions. In such cases, promptly discontinue JENTADUETO XR, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. (5.5)
- Vitamin B₁₂ deficiency: Metformin may lower vitamin B₁₂ levels. Monitor hematologic parameters annually. (5.6)
- Arthralgia: Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue drug if appropriate. (5.7)
- Bullous pemphigoid: There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients taking DPP-4 inhibitors. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue JENTADUETO XR. (5.8)
- Macrovascular outcomes: No conclusive evidence of macrovascular risk reduction with JENTADUETO XR (5.9)

ADVERSE REACTIONS

- Adverse reactions reported in ≥5% of patients treated with linagliptin and metformin coadministered and more commonly than in patients treated with placebo are nasopharyngitis and diarrhea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or 1-800-459-9906 TTY, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Carbonic anhydrase inhibitors may increase risk of lactic acidosis. Consider more frequent monitoring. (7.1)
- Drugs that reduce metformin clearance (such as ranolazine, vandetanib, dolutegravir, and cimetidine) may increase the accumulation of metformin. Consider the benefits and risks of concomitant use. (7.1)
- Alcohol can potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake. (7.1)
- Strong P-glycoprotein/CYP3A4 inducer: Efficacy may be reduced when administered in combination (e.g., rifampin). Use of alternative treatments is strongly recommended. (7.2)

USE IN SPECIFIC POPULATIONS

- Females and Males of Reproductive Potential: Advise premenopausal females of the potential for an unintended pregnancy. (8.3)
- Geriatric Use: Assess renal function more frequently. (8.5)
- Hepatic Impairment: Avoid use in patients with hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS

Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL [see *Warnings and Precautions (5.1)*].

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

Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the full prescribing information [see *Dosage and Administration (2.2)*, *Contraindications (4)*, *Warnings and Precautions (5.1)*, *Drug Interactions (7.1)*, and *Use in Specific Populations (8.6, 8.7)*].

If metformin-associated lactic acidosis is suspected, immediately discontinue JENTADUETO XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended [see *Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

1.1 Indication

JENTADUETO XR is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate [see *Dosage and Administration (2.1)* and *Clinical Studies (14.1)*].

1.2 Important Limitations of Use

JENTADUETO XR should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

JENTADUETO XR has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at an increased risk for the development of pancreatitis while using JENTADUETO XR [see *Warnings and Precautions (5.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The dosage of JENTADUETO XR should be individualized on the basis of both effectiveness and tolerability, while not exceeding the maximum recommended total daily dose of linagliptin 5 mg and metformin hydrochloride 2000 mg. JENTADUETO XR should be given once daily with a meal. For available dosage forms and strengths [see *Dosage Forms and Strengths (3)*].

Recommended starting dose:

- In patients currently not treated with metformin, initiate JENTADUETO XR treatment with 5 mg linagliptin/1000 mg metformin hydrochloride extended-release once daily with a meal.
- In patients already treated with metformin, start JENTADUETO XR with 5 mg of linagliptin total daily dose and a similar total daily dose of metformin once daily with a meal.
- In patients already treated with linagliptin and metformin or JENTADUETO, switch to JENTADUETO XR containing 5 mg of linagliptin total daily dose and a similar total daily dose of metformin once daily with a meal.

JENTADUETO XR should be swallowed whole. The tablets must not be split, crushed, dissolved, or chewed before swallowing. There have been reports of incompletely dissolved tablets being eliminated in the feces for other tablets containing metformin extended-release. If a patient reports seeing tablets in feces, the healthcare provider should assess adequacy of glycemic control.

JENTADUETO XR 5 mg linagliptin/1000 mg metformin hydrochloride extended-release tablet should be taken as a single tablet once daily. Patients using 2.5 mg linagliptin/1000 mg metformin extended-release tablets should take two tablets together once daily.

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

2.2 Recommended Dosing in Renal Impairment

Assess renal function prior to initiation of JENTADUETO XR and periodically thereafter.

JENTADUETO XR is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m².

Initiation of JENTADUETO XR in patients with an eGFR between 30-45 mL/min/1.73 m² is not recommended.

In patients taking JENTADUETO XR whose eGFR later falls below 45 mL/min/1.73 m², assess benefit risk of continuing therapy.

Discontinue JENTADUETO XR if the patient's eGFR later falls below 30 mL/min/1.73 m² [see *Contraindications (4)* and *Warnings and Precautions (5.1)*].

2.3 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue JENTADUETO XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m²; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart JENTADUETO XR if renal function is stable [see *Warnings and Precautions (5.1)*].

3 DOSAGE FORMS AND STRENGTHS

JENTADUETO XR is a combination of linagliptin and extended-release metformin hydrochloride. JENTADUETO XR tablets are available in the following dosage forms and strengths:

- 5 mg/1000 mg are white, oval-shaped coated tablets with one side printed in black ink with the Boehringer Ingelheim logo and “D5” on the top line and “1000M” on the bottom line.
- 2.5 mg /1000 mg are yellow, oval-shaped coated tablets with one side printed in black ink with the Boehringer Ingelheim logo and “D2” on the top line and “1000M” on the bottom line.

4 CONTRAINDICATIONS

JENTADUETO XR is contraindicated in patients with:

- Severe renal impairment (eGFR below 30 mL/min/1.73 m²) [see *Warnings and Precautions (5.1)*]
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin [see *Warnings and Precautions (5.1)*]
- A history of hypersensitivity reaction to linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity [see *Warnings and Precautions (5.5) and Adverse Reactions (6.1)*]
- Hypersensitivity to metformin

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

Metformin

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

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

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

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

Renal Impairment: The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient’s renal function include [see *Dosage and Administration (2.2), Clinical Pharmacology (12.3)*]:

- Before initiating JENTADUETO XR, obtain an estimated glomerular filtration rate (eGFR).
- JENTADUETO XR is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m² [see *Contraindications (4)*].
- Initiation of JENTADUETO XR is not recommended in patients with eGFR between 30 – 45 mL/min/1.73 m².
- Obtain an eGFR at least annually in all patients taking JENTADUETO XR. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.
- In patients taking JENTADUETO XR whose eGFR later falls below 45 mL/min/1.73 m², assess the benefit and risk of continuing therapy.

Drug Interactions: The concomitant use of JENTADUETO XR with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation (e.g., cationic drugs) [see *Drug Interactions (7.1)*]. Therefore, consider more frequent monitoring of patients.

Age 65 or Greater: The risk of metformin-associated lactic acidosis increases with the patient’s age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients [see *Use in Specific Populations (8.5)*].

Radiological Studies with Contrast: Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop JENTADUETO XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m²; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart JENTADUETO XR if renal function is stable.

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

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

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

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

5.2 Pancreatitis

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

5.3 Heart Failure

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

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

5.4 Use with Medications Known to Cause Hypoglycemia

Linagliptin

Insulin secretagogues and insulin are known to cause hypoglycemia. The use of linagliptin in combination with an insulin secretagogue (e.g., sulfonylurea) was associated with a higher rate of hypoglycemia compared with placebo in a clinical trial [see *Adverse Reactions (6.1)*]. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with JENTADUETO XR [see *Drug Interactions (7.3)*].

Metformin

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as SUs and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking β -adrenergic blocking drugs.

5.5 Hypersensitivity Reactions

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

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

5.6 Vitamin B₁₂ Levels

In controlled, 29-week clinical trials of metformin a decrease to subnormal levels of previously normal serum vitamin B₁₂ levels, without clinical manifestations, was observed in approximately 7% of metformin-treated patients. Such decrease, possibly due to interference with B₁₂ absorption from the B₁₂-intrinsic factor complex, is, however, very rarely associated with anemia or neurologic manifestations due to the short duration (<1 year) of the clinical trials. This risk may be more relevant to patients receiving long-term treatment with metformin, and adverse hematologic and neurologic reactions have been reported postmarketing. The decrease in vitamin B₁₂ levels appears to be rapidly reversible with discontinuation of metformin or vitamin B₁₂ supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on JENTADUETO XR and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate vitamin B₁₂ or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B₁₂ levels. In these patients, routine serum vitamin B₁₂ measurement at 2- to 3-year intervals may be useful.

5.7 Severe and Disabling Arthralgia

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

5.8 Bullous Pemphigoid

Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving JENTADUETO XR. If bullous pemphigoid is suspected, JENTADUETO XR should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

5.9 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with linagliptin or metformin.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

Linagliptin/Metformin

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

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

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

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

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

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

Linagliptin

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

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

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

Metformin

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

In a 24-week clinical trial in which extended-release metformin or placebo was added to glyburide therapy, the most common ($>5\%$ and greater than placebo) adverse reactions in the combined treatment group were hypoglycemia (13.7% vs 4.9%), diarrhea (12.5% vs 5.6%), and nausea (6.7% vs 4.2%).

Hypoglycemia

Linagliptin/Metformin

In a 24-week factorial design study, hypoglycemia was reported in 4 (1.4%) of 286 subjects treated with linagliptin + metformin, 6 (2.1%) of 291 subjects treated with metformin, and 1 (1.4%) of 72 subjects treated with placebo. When linagliptin was administered in combination with metformin and a sulfonylurea, 181 (22.9%) of 792 patients reported hypoglycemia compared with 39 (14.8%) of 263 patients administered placebo in combination with metformin and sulfonylurea. Adverse reactions of hypoglycemia were based on all reports of hypoglycemia. A concurrent glucose measurement was not required or was normal in some patients. Therefore, it is not possible to conclusively determine that all these reports reflect true hypoglycemia.

Laboratory Tests

Linagliptin

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

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

Metformin

Decrease in Vitamin B₁₂ Absorption: Long-term treatment with metformin has been associated with a decrease in vitamin B₁₂ absorption which may very rarely result in clinically significant vitamin B₁₂ deficiency (e.g., megaloblastic anemia) [see *Warnings and Precautions* (5.6)].

6.2 Postmarketing Experience

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

Linagliptin

- Acute pancreatitis, including fatal pancreatitis [see *Indications and Usage* (1.2) and *Warnings and Precautions* (5.2)]
- Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions [see *Warnings and Precautions* (5.5)]
- Severe and disabling arthralgia [see *Warnings and Precautions* (5.7)]
- Bullous pemphigoid [see *Warnings and Precautions* (5.8)]
- Rash
- Mouth ulceration, stomatitis
- Rhabdomyolysis

Metformin

- Cholestatic, hepatocellular, and mixed hepatocellular liver injury

7 DRUG INTERACTIONS

7.1 Drug Interactions with Metformin

Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with JENTADUETO XR, may increase the risk of lactic acidosis. Consider more frequent monitoring of these patients [see *Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)*].

Drugs that Reduce Metformin Clearance

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis [see *Clinical Pharmacology (12.3)*]. Consider the benefits and risks of concomitant use.

Alcohol

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

7.2 Drug Interactions with Linagliptin

Inducers of P-glycoprotein and CYP3A4 Enzymes

Rifampin decreased linagliptin exposure, suggesting that the efficacy of linagliptin may be reduced when administered in combination with a strong P-gp inducer or CYP 3A4 inducer. As JENTADUETO XR is a fixed-dose combination of linagliptin and metformin, use of alternative treatments (not containing linagliptin) is strongly recommended when concomitant treatment with a strong P-gp or CYP 3A4 inducer is necessary [see *Clinical Pharmacology (12.3)*].

7.3 Insulin Secretagogues or Insulin

Coadministration of JENTADUETO XR with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.

7.4 Drugs Affecting Glycemic Control

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving JENTADUETO XR, the patient should be closely observed to maintain adequate glycemic control [see *Clinical Pharmacology (12.3)*]. When such drugs are withdrawn from a patient receiving JENTADUETO XR, the patient should be observed closely for hypoglycemia.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited data with JENTADUETO XR and linagliptin use in pregnant women are not sufficient to inform a JENTADUETO XR-associated or linagliptin-associated risk for major birth defects and miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk [see *Data*]. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy [see *Clinical Considerations*].

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

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

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Data

Human Data

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

Animal Data

Linagliptin and metformin, the components of JENTADUETO XR, were coadministered to pregnant Wistar Han rats during the period of organogenesis. No adverse developmental outcome was observed at doses similar to the maximum recommended clinical dose, based on exposure. At higher doses associated with maternal toxicity, the metformin component of the combination was associated with an increased incidence of fetal rib and scapula malformations at ≥ 9 -times a 2000 mg clinical dose, based on exposure.

Linagliptin

No adverse developmental outcome was observed when linagliptin was administered to pregnant Wistar Han rats and Himalayan rabbits during the period of organogenesis at doses up to 240 mg/kg and 150 mg/kg, respectively. These doses represent approximately 943 times (rats) and 1943 times (rabbits) the 5 mg clinical dose, based on exposure. No adverse functional, behavioral, or reproductive outcome was observed in offspring following administration of linagliptin to Wistar Han rats from gestation day 6 to lactation day 21 at a dose 49 times the 5 mg clinical dose, based on exposure.

Metformin Hydrochloride:

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

8.2 Lactation

Risk Summary

There is no information regarding the presence of JENTADUETO XR or linagliptin in human milk, the effects on the breastfed infant, or the effects on milk production. However, linagliptin is present in rat milk. Limited published studies report that metformin is present in human milk [see *Data*]. However, there is insufficient

information to determine the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for JENTADUETO XR and any potential adverse effects on the breastfed child from JENTADUETO XR or from the underlying maternal condition.

Data

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

8.3 Females and Males of Reproductive Potential

Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

8.4 Pediatric Use

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

8.5 Geriatric Use

Linagliptin is minimally excreted by the kidney; however, metformin is substantially excreted by the kidney [see *Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)*].

Linagliptin

There were 4040 type 2 diabetes patients treated with linagliptin 5 mg from 15 clinical trials of linagliptin; 1085 (27%) patients were 65 years and over, while 131 (3%) were 75 years and over. Of these patients, 2566 were enrolled in 12 double-blind placebo-controlled studies; 591 (23%) were 65 years and over, while 82 (3%) were 75 years and over. No overall differences in safety or effectiveness were observed between patients 65 years and over and younger patients. Therefore, no dose adjustment is recommended in the elderly population. While clinical studies of linagliptin have not identified differences in response between the elderly and younger patients, 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, although other reported clinical experience has not identified differences in responses between the elderly and young patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients [see *Contraindications (4), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)*].

8.6 Renal Impairment

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. JENTADUETO XR is contraindicated in severe renal impairment: patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m² [see *Dosage and Administration (2.2), Contraindications (4), Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)*].

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

8.7 Hepatic Impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. JENTADUETO XR is not recommended in patients with hepatic impairment [see *Warnings and Precautions (5.1)*].

10 OVERDOSAGE

In the event of an overdose with JENTADUETO XR, contact the Poison Control Center. Employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal of linagliptin by hemodialysis or peritoneal dialysis is unlikely. However, metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful partly for removal of accumulated metformin from patients in whom JENTADUETO XR overdose is suspected.

Linagliptin

During controlled clinical trials in healthy subjects, with single doses of up to 600 mg of linagliptin (equivalent to 120 times the recommended daily dose), there were no dose-related clinical adverse drug reactions. There is no experience with doses above 600 mg in humans.

Metformin

Overdose of metformin has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases [see *Boxed Warning and Warnings and Precautions (5.1)*].

11 DESCRIPTION

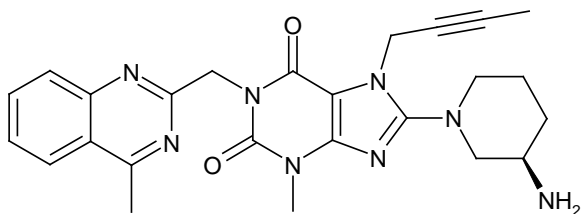
JENTADUETO XR tablets contain 2 oral antihyperglycemic drugs used in the management of type 2 diabetes mellitus: linagliptin and metformin hydrochloride.

Linagliptin

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

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

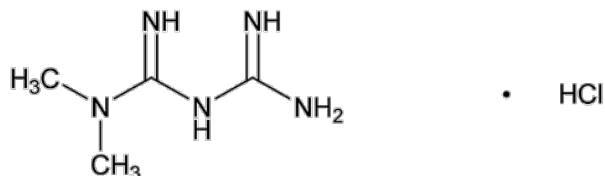
The empirical formula is C₂₅H₂₈N₈O₂ and the molecular weight is 472.54 g/mol. The structural formula is:



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

Metformin Hydrochloride

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



JENTADUETO XR consists of an extended-release metformin core tablet that is coated with the immediate-release drug substance linagliptin. JENTADUETO XR is available for oral administration as tablets containing 5 mg linagliptin and 1000 mg metformin hydrochloride extended-release (JENTADUETO XR 5 mg/1000 mg) or 2.5 mg linagliptin and 1000 mg metformin hydrochloride extended-release (JENTADUETO XR 2.5 mg/1000 mg). Each coated tablet of JENTADUETO XR contains the following inactive ingredients: Tablet core: polyethylene oxide, hypromellose, and magnesium stearate. Coating: hydroxypropyl cellulose, hypromellose, talc, titanium dioxide, arginine, polyethylene glycol, ferric oxide yellow (2.5 mg/1000 mg), carnauba wax, ferrous ferric oxide, propylene glycol, and isopropyl alcohol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

JENTADUETO XR

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

Linagliptin

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

Metformin

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike SUs, metformin does not produce hypoglycemia in either patients with type 2 diabetes mellitus or normal subjects (except in special circumstances) [see *Warnings and Precautions (5.4)*] 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.

12.2 Pharmacodynamics

Linagliptin

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

Cardiac Electrophysiology

In a randomized, placebo-controlled, active-comparator, 4-way crossover study, 36 healthy subjects were administered a single oral dose of linagliptin 5 mg, linagliptin 100 mg (20 times the recommended dose), moxifloxacin, and placebo. No increase in QTc was observed with either the recommended dose of 5 mg or the 100-mg dose. At the 100-mg dose, peak linagliptin plasma concentrations were approximately 38-fold higher than the peak concentrations following a 5-mg dose.

12.3 Pharmacokinetics

JENTADUETO XR

Administration of JENTADUETO XR with a high-fat meal resulted in up to 7-22% decrease in overall exposure (AUC_{0-72}) of linagliptin; this effect is not clinically relevant. For metformin extended-release, high-fat meals increased systemic exposure (AUC_{0-tz}) by approximately 54-71% relative to fasting, while C_{max} is increased up to 11%. Meals prolonged T_{max} by approximately 3 hours.

Absorption

Linagliptin

The absolute bioavailability of linagliptin is approximately 30%. Following oral administration, plasma concentrations of linagliptin decline in at least a biphasic manner with a long terminal half-life (>100 hours), related to the saturable binding of linagliptin to DPP-4. However, the prolonged elimination does not contribute to the accumulation of the drug. The effective half-life for accumulation of linagliptin, as determined from oral administration of multiple doses of linagliptin 5 mg, is approximately 12 hours. After once-daily dosing, steady state plasma concentrations of linagliptin 5 mg are reached by the third dose, and C_{max} and AUC increased by a factor of 1.3 at steady-state compared with the first dose. Plasma AUC of linagliptin increased in a less than dose-proportional manner in the dose range of 1 to 10 mg. The pharmacokinetics of linagliptin is similar in healthy subjects and in patients with type 2 diabetes.

Metformin

Following a single oral dose of 1000 mg (2 x 500 mg tablets) metformin extended-release after a meal, the time to reach maximum plasma metformin concentration (T_{max}) is achieved at approximately 7 to 8 hours. In both single- and multiple-dose studies in healthy subjects, once daily 1000 mg (2 x 500 mg tablets) dosing provides equivalent systemic exposure, as measured by AUC, and up to 35% higher C_{max} of metformin relative to the immediate-release given as 500 mg twice daily.

Single oral doses of metformin extended-release from 500 mg to 2500 mg resulted in less than proportional increase in both AUC and C_{max} . Low-fat and high-fat meals increased the systemic exposure (as measured by AUC) from metformin extended-release tablets by about 38% and 73%, respectively, relative to fasting. Both meals prolonged metformin T_{max} by approximately 3 hours but C_{max} was not affected.

Distribution

Linagliptin

The mean apparent volume of distribution at steady state following a single intravenous dose of linagliptin 5 mg to healthy subjects is approximately 1110 L, indicating that linagliptin extensively distributes to the tissues. Plasma protein binding of linagliptin is concentration-dependent decreasing from about 99% at 1 nmol/L to 75% to 89% at ≥ 30 nmol/L, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin. At high concentrations, where DPP-4 is fully saturated, 70% to 80% of linagliptin remains bound to plasma proteins and 20% to 30% is unbound in plasma. Plasma binding is not altered in patients with renal or hepatic impairment.

Metformin

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

Metabolism

Linagliptin

Following oral administration, the majority (about 90%) of linagliptin is excreted unchanged, indicating that metabolism represents a minor elimination pathway. A small fraction of absorbed linagliptin is metabolized to a pharmacologically inactive metabolite, which shows a steady-state exposure of 13.3% relative to linagliptin.

Metformin

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

Excretion

Linagliptin

Following administration of an oral [14 C] linagliptin dose to healthy subjects, approximately 85% of the administered radioactivity was eliminated via the enterohepatic system (80%) or urine (5%) within 4 days of dosing. Renal clearance at steady state 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.

Specific Populations

Renal Impairment

JENTADUETO XR: Studies characterizing the pharmacokinetics of linagliptin and metformin after administration of *JENTADUETO XR* in renally impaired patients have not been performed [see *Contraindications (4) and Warnings and Precautions (5.1)*].

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

Metformin: In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased [see *Contraindications (4) and Warnings and Precautions (5.1)*].

Hepatic Impairment

JENTADUETO XR: Studies characterizing the pharmacokinetics of linagliptin and metformin after administration of *JENTADUETO XR* in hepatically impaired patients have not been performed [see *Warnings and Precautions (5.1)*].

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

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

Body Mass Index (BMI)/Weight

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

Gender

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

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

Geriatric

JENTADUETO XR: Studies characterizing the pharmacokinetics of linagliptin and metformin after administration of JENTADUETO XR in geriatric patients have not been performed [see *Warnings and Precautions (5.1) and Use in Specific Populations (8.5)*].

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

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

Pediatric

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

Race

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

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

Drug Interactions

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

Linagliptin

In vitro Assessment of Drug Interactions

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

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

In vivo Assessment of Drug Interactions

Strong inducers of CYP3A4 or P-gp (e.g., rifampin) decrease exposure to linagliptin to subtherapeutic and likely ineffective concentrations. For patients requiring use of such drugs, an alternative to linagliptin is strongly recommended. *In vivo* studies indicated evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-gp, and OCT. No dose adjustment of linagliptin is recommended based on results of the described pharmacokinetic studies.

Table 2 Effect of Coadministered Drugs on Systemic Exposure of Linagliptin

Coadministered Drug	Dosing of Coadministered Drug*	Dosing of Linagliptin*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect=1.0	
			AUC [†]	C _{max}
No dosing adjustments required for linagliptin when given with the following coadministered drugs:				
Metformin	850 mg TID	10 mg QD	1.20	1.03
Glyburide	1.75 mg [#]	5 mg QD	1.02	1.01
Pioglitazone	45 mg QD	10 mg QD	1.13	1.07
Ritonavir	200 mg BID	5 mg [#]	2.01	2.96
The efficacy of JENTADUETO XR may be reduced when administered in combination with strong inducers of CYP3A4 or P-gp (e.g., rifampin). Use of alternative treatments is strongly recommended [see <i>Drug Interactions (7.2)</i>].				
Rifampin	600 mg QD	5 mg QD	0.60	0.56

*Multiple dose (steady state) unless otherwise noted

[#] Single dose

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

QD = once daily

BID = twice daily

TID = three times daily

Table 3 Effect of Linagliptin on Systemic Exposure of Coadministered Drugs

Coadministered Drug	Dosing of Coadministered Drug*	Dosing of Linagliptin*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect=1.0		
				AUC [†]	C _{max}
No dosing adjustments required for the following coadministered drugs:					
Metformin	850 mg TID	10 mg QD	metformin	1.01	0.89
Glyburide	1.75 mg [#]	5 mg QD	glyburide	0.86	0.86
Pioglitazone	45 mg QD	10 mg QD	pioglitazone metabolite M-III metabolite M-IV	0.94 0.98 1.04	0.86 0.96 1.05
Digoxin	0.25 mg QD	5 mg QD	digoxin	1.02	0.94
Simvastatin	40 mg QD	10 mg QD	simvastatin simvastatin acid	1.34 1.33	1.10 1.21
Warfarin	10 mg [#]	5 mg QD	R-warfarin S-warfarin INR PT	0.99 1.03 0.93** 1.03**	1.00 1.01 1.04** 1.15**
Ethinylestradiol and levonorgestrel	ethinylestradiol 0.03 mg and levonorgestrel 0.150 mg QD	5 mg QD	ethinylestradiol levonorgestrel	1.01 1.09	1.08 1.13

* Multiple dose (steady state) unless otherwise noted

[#] Single dose

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

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

INR = International Normalized Ratio

PT = Prothrombin Time

QD = once daily

TID = three times daily

Metformin hydrochloride

Table 4 Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

Coadministered Drug	Dosing of Coadministered Drug*	Dosing of Metformin*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect=1.0		
				AUC [†]	C _{max}
No dosing adjustments required for the following coadministered drugs:					
Glyburide	5 mg	500 mg ≠	metformin	0.98‡	0.99‡
Furosemide	40 mg	850 mg	metformin	1.09‡	1.22‡
Nifedipine	10 mg	850 mg	metformin	1.16	1.21
Propranolol	40 mg	850 mg	metformin	0.90	0.94
Ibuprofen	400 mg	850 mg	metformin	1.05‡	1.07‡
Drugs that are eliminated by renal tubular secretion may reduce metformin elimination: [see Warnings and Precautions (5.1) and Drug Interactions (7.1)].					
Cimetidine	400 mg	850 mg	metformin	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis: [see Warnings and Precautions (5.1) and Drug Interactions (7.1)].					
Topiramate**	100 mg	500 mg	metformin	1.25	1.17

* All metformin and coadministered drugs were given as single doses

[†] AUC = AUC(INF)

≠ metformin hydrochloride extended-release tablets 500 mg

‡ Ratio of arithmetic means

**At steady state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours; AUC = AUC0-12h

Table 5 Effect of Metformin on Coadministered Drug Systemic Exposure

Coadministered Drug	Dosing of Coadministered Drug*	Dosing of Metformin*	Geometric Mean Ratio (ratio with/without metformin) No effect=1.0		
				AUC [†]	C _{max}
No dosing adjustments required for the following coadministered drugs:					
Glyburide	5 mg	500 mg§	glyburide	0.78‡	0.63‡
Furosemide	40 mg	850 mg	furosemide	0.87‡	0.69‡
Nifedipine	10 mg	850 mg	nifedipine	1.10§	1.08
Propranolol	40 mg	850 mg	propranolol	1.01§	0.94
Ibuprofen	400 mg	850 mg	ibuprofen	0.97¶	1.01¶
Cimetidine	400 mg	850 mg	cimetidine	0.95§	1.01

* All metformin and coadministered drugs were given as single doses

† AUC = AUC(INF) unless otherwise noted

‡ Ratio of arithmetic means, p-value of difference <0.05

§ AUC(0-24 hr) reported

¶ Ratio of arithmetic means

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

JENTADUETO XR

No animal studies have been conducted with the combined products in JENTADUETO XR to evaluate carcinogenesis, mutagenesis, or impairment of fertility. General toxicity studies in rats up to 13 weeks were performed with linagliptin/metformin coadministered.

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

Linagliptin

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

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

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

Metformin Hydrochloride

Long-term carcinogenicity studies have been performed in Sprague Dawley rats at doses of 150, 300, and 450 mg/kg/day in males and 150, 450, 900, and 1200 mg/kg/day in females. These doses are both approximately 2, 4, and 8 times in males, and 3, 7, 12, and 16 times in females of the maximum recommended human daily dose of 2000 mg/kg/day based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female rats. A carcinogenicity study was also performed in Tg.AC transgenic mice at doses of up to 2000 mg/kg/day applied dermally. No evidence of carcinogenicity was observed in male or female mice.

Genotoxicity assessments in the Ames test, gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes) and *in vivo* mouse micronucleus tests were negative.

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

14 CLINICAL STUDIES

The safety and efficacy of JENTADUETO XR have been established based on adequate and well-controlled studies of linagliptin and metformin coadministered in patients with type 2 diabetes mellitus inadequately controlled on diet and exercise and in combination with sulfonylurea.

14.1 Initial Combination Therapy with Linagliptin and Metformin

A total of 791 patients with type 2 diabetes mellitus and inadequate glycemic control on diet and exercise participated in the 24-week, randomized, double-blind, portion of this placebo-controlled factorial study designed to assess the efficacy of linagliptin as initial therapy with metformin. Patients on an antihyperglycemic agent (52%) underwent a drug washout period of 4 weeks' duration. After the washout period and after completing a 2-week single-blind placebo run-in period, patients with inadequate glycemic control (A1C ≥7.0% to ≤10.5%) were randomized. Patients with inadequate glycemic control (A1C ≥7.5% to <11.0%) not on antihyperglycemic agents at study entry (48%) immediately entered the 2-week single-blind placebo run-in period and then were randomized. Randomization was stratified by baseline A1C (<8.5% vs ≥8.5%) and use of a prior oral antidiabetic drug (none vs monotherapy). Patients were randomized in a 1:2:2:2:2 ratio to either placebo or one of 5 active-treatment arms. Approximately equal numbers of patients were randomized to receive initial therapy with 5 mg of linagliptin once daily, 500 mg or 1000 mg of metformin twice daily, or 2.5 mg of linagliptin twice daily in combination with 500 mg or 1000 mg of metformin twice daily. Patients who failed to meet specific glycemic goals during the study were treated with sulfonylurea, thiazolidinedione, or insulin rescue therapy.

Initial therapy with the combination of linagliptin and metformin provided significant improvements in A1C, and fasting plasma glucose (FPG) compared to placebo, to metformin alone, and to linagliptin alone (Table 6, Figure 1). The adjusted mean treatment difference in A1C from baseline to week 24 (LOCF) was -0.5% (95% CI -0.7, -0.3; p<0.0001) for linagliptin 2.5 mg/metformin 1000 mg twice daily compared to metformin 1000 mg twice daily; -1.1% (95% CI -1.4, -0.9; p<0.0001) for linagliptin 2.5 mg/metformin 1000 mg twice daily compared to linagliptin 5 mg once daily; -0.6% (95% CI -0.8, -0.4; p<0.0001) for linagliptin 2.5 mg/metformin 500 mg twice daily compared to metformin 500 mg twice daily; and -0.8% (95% CI -1.0, -0.6; p<0.0001) for linagliptin 2.5 mg/metformin 500 mg twice daily compared to linagliptin 5 mg once daily.

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

Table 6 Glycemic Parameters at Final Visit (24-Week Study) for Linagliptin and Metformin, Alone and in Combination in Randomized Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Diet and Exercise**

	Placebo	Linagliptin 5 mg Once Daily*	Metformin 500 mg Twice Daily	Linagliptin 2.5 mg Twice Daily* + Metformin 500 mg Twice Daily	Metformin 1000 mg Twice Daily	Linagliptin 2.5 mg Twice Daily* + Metformin 1000 mg Twice Daily
A1C (%)						
Number of patients	n=65	n=135	n=141	n=137	n=138	n=140
Baseline (mean)	8.7	8.7	8.7	8.7	8.5	8.7
Change from baseline (adjusted mean****)	0.1	-0.5	-0.6	-1.2	-1.1	-1.6
Difference from placebo (adjusted mean) (95% CI)	--	-0.6 (-0.9, -0.3)	-0.8 (-1.0, -0.5)	-1.3 (-1.6, -1.1)	-1.2 (-1.5, -0.9)	-1.7 (-2.0, -1.4)
Patients [n (%)] achieving A1C <7%***	7 (10.8)	14 (10.4)	26 (18.6)	41 (30.1)	42 (30.7)	74 (53.6)
Patients (%) receiving rescue medication	29.2	11.1	13.5	7.3	8.0	4.3
FPG (mg/dL)						
Number of patients	n=61	n=134	n=136	n=135	n=132	n=136
Baseline (mean)	203	195	191	199	191	196
Change from baseline (adjusted mean****)	10	-9	-16	-33	-32	-49
Difference from placebo (adjusted mean) (95% CI)	--	-19 (-31, -6)	-26 (-38, -14)	-43 (-56, -31)	-42 (-55, -30)	-60 (-72, -47)

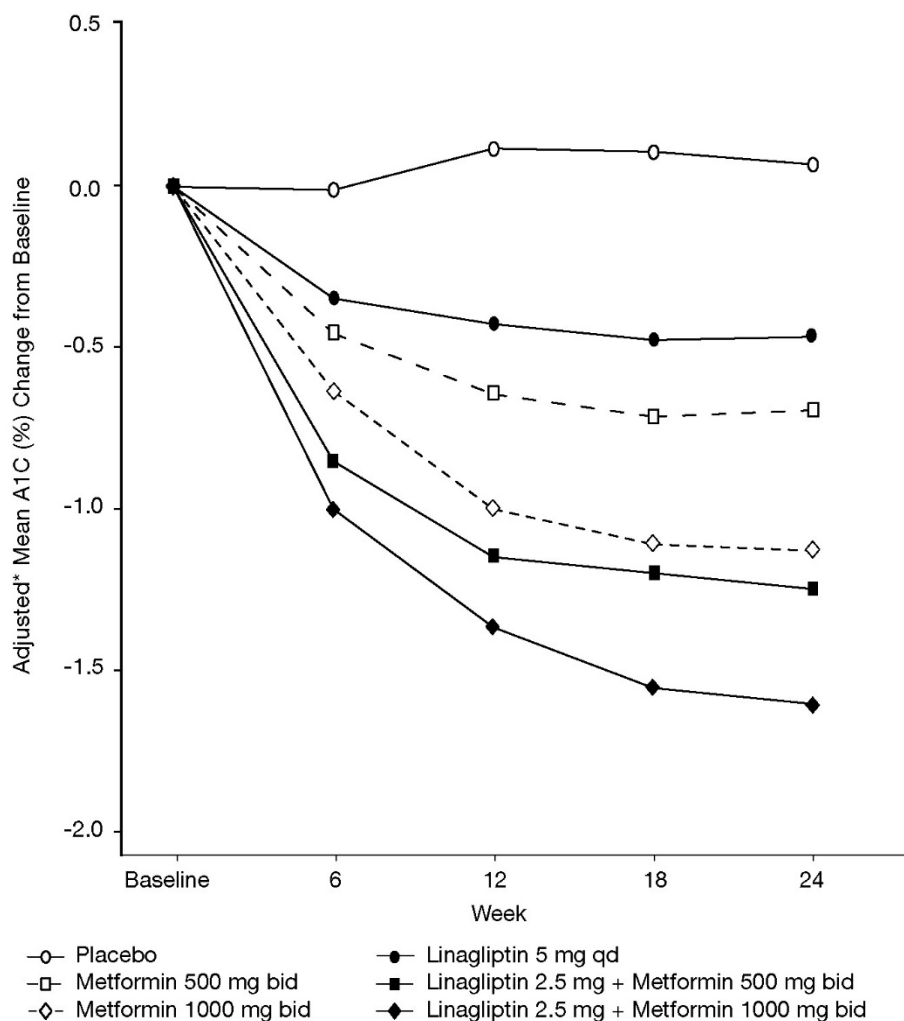
*Total daily dose of linagliptin is equal to 5 mg

**Full analysis population using last observation on study

***Metformin 500 mg twice daily, n=140; Linagliptin 2.5 mg twice daily + Metformin 500 mg twice daily, n=136; Metformin 1000 mg twice daily, n=137; Linagliptin 2.5 mg twice daily + Metformin 1000 mg twice daily, n=138

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

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



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

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

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

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

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

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

[†]p<0.0001 compared to linagliptin, ^{††}p=0.0054 compared to linagliptin

*Full analysis set population

**A1C: MMRM model included treatment, continuous baseline A1C, baseline A1C by visit interaction, visit by treatment interaction, baseline renal impairment by treatment interaction and baseline renal impairment by treatment by visit interaction. FPG: MMRM model included treatment, continuous baseline A1C, continuous

baseline FPG, baseline FPG by visit interaction, visit by treatment interaction, baseline renal impairment by treatment interaction and baseline renal impairment by treatment by visit interaction.

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

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

14.3 Add-On Combination Therapy with Metformin

A total of 701 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of linagliptin in combination with metformin. Patients already on metformin (n=491) at a dose of at least 1500 mg per day were randomized after completing a 2-week, open-label, placebo run-in period. Patients on metformin and another antihyperglycemic agent (n=207) were randomized after a run-in period of approximately 6 weeks on metformin (at a dose of at least 1500 mg per day) in monotherapy. Patients were randomized to the addition of either linagliptin 5 mg or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with glimepiride rescue.

In combination with metformin, linagliptin provided statistically significant improvements in A1C, FPG, and 2-hour PPG compared with placebo (Table 8). Rescue glycemic therapy was used in 7.8% of patients treated with linagliptin 5 mg and in 18.9% of patients treated with placebo. A similar decrease in body weight was observed for both treatment groups.

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

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

* Full analysis population using last observation on study

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

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

14.4 Active-Controlled Study vs Glimepiride in Combination with Metformin

The efficacy of linagliptin was evaluated in a 104-week double-blind, glimepiride-controlled non-inferiority study in type 2 diabetic patients with insufficient glycemic control despite metformin therapy. Patients being treated with metformin only entered a run-in period of 2 weeks' duration, whereas patients pretreated with metformin and one additional antihyperglycemic agent entered a run-in treatment period of 6 weeks' duration with metformin monotherapy (dose of ≥ 1500 mg per day) and washout of the other agent. After an additional 2-week placebo run-in period, those with inadequate glycemic control (A1C 6.5% to 10%) were randomized 1:1 to the addition of linagliptin 5 mg once daily or glimepiride. Randomization was stratified by baseline HbA1c (<8.5% vs $\geq 8.5\%$), and the previous use of antidiabetic drugs (metformin alone vs metformin plus one other OAD). Patients receiving glimepiride were given an initial dose of 1 mg/day and then electively titrated over the next 12 weeks to a maximum dose of 4 mg/day as needed to optimize glycemic control. Thereafter, the glimepiride dose was to be kept constant, except for down-titration to prevent hypoglycemia.

After 52 weeks and 104 weeks, linagliptin and glimepiride both had reductions from baseline in A1C (52 weeks: -0.4% for linagliptin, -0.6% for glimepiride; 104 weeks: -0.2% for linagliptin, -0.4% for glimepiride) from a baseline mean of 7.7% (Table 9). The mean difference between groups in A1C change from baseline was 0.2% with 2-sided 97.5% confidence interval (0.1%, 0.3%) for the intent-to-treat population using last observation carried forward. These results were consistent with the completers analysis.

Table 9 Glycemic Parameters at 52 and 104 Weeks in Study Comparing Linagliptin to Glimperide as Add-On Therapy in Patients Inadequately Controlled on Metformin**

	Week 52		Week 104	
	Linagliptin 5 mg + Metformin	Glimperide + Metformin (mean glimepiride dose 3 mg)	Linagliptin 5 mg + Metformin	Glimperide + Metformin (mean glimepiride dose 3 mg)
A1C (%)				
Number of patients	n=764	n=755	n=764	n=755
Baseline (mean)	7.7	7.7	7.7	7.7
Change from baseline (adjusted mean***)	-0.4	-0.6	-0.2	-0.4
Difference from glimepiride (adjusted mean) (97.5% CI)	0.2 (0.1, 0.3)	--	0.2 (0.1, 0.3)	--
FPG (mg/dL)				
Number of patients	n=733	n=725	n=733	n=725
Baseline (mean)	164	166	164	166
Change from baseline (adjusted mean***)	-8*	-15	-2 [†]	-9

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

**Full analysis population using last observation on study

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

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

14.5 Add-On Combination Therapy with Metformin and a Sulfonylurea

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

In combination with a sulfonylurea and metformin, linagliptin provided statistically significant improvements in A1C and FPG compared with placebo (Table 10). In the entire study population (patients on linagliptin in combination with a sulfonylurea and metformin), a mean reduction from baseline relative to placebo in A1C of -0.6% and in FPG of -13 mg/dL was seen. Rescue therapy was used in 5.4% of patients treated with linagliptin 5 mg and in 13% of patients treated with placebo. Change from baseline in body weight did not differ significantly between the groups.

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

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

SU=sulfonylurea

*Full analysis population using last observation on study

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

JENTADUETO XR (linagliptin and metformin hydrochloride extended-release) tablets 5 mg/1000 mg, white, oval-shaped coated tablets with one side printed in black ink with the Boehringer Ingelheim logo and "D5" on the top line and "1000M" on the bottom line, are supplied as follows:

Bottles of 30 (NDC 0597-0275-33)

Bottles of 90 (NDC 0597-0275-81)

JENTADUETO XR (linagliptin and metformin hydrochloride extended-release) tablets 2.5 mg/1000 mg, yellow, oval-shaped coated tablets with one side printed in black ink with the Boehringer Ingelheim logo and "D2" on the top line and "1000M" on the bottom line, are supplied as follows:

Bottles of 60 (NDC 0597-0270-73)

Bottles of 180 (NDC 0597-0270-94)

Storage

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Protect from exposure to high humidity. Store in a safe place out of reach of children.

17 PATIENT COUNSELING INFORMATION

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

Medication Guide

Instruct patients to read the Medication Guide before starting JENTADUETO XR therapy and to reread each time the prescription is renewed. Instruct patients to inform their doctor if they develop any bothersome or unusual symptoms, or if any symptom persists or worsens.

Inform patients of the potential risks and benefits of JENTADUETO XR and of alternative modes of therapy. Also inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and A1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

Lactic Acidosis

Inform patients of the risks of lactic acidosis due to the metformin component, its symptoms, and conditions that predispose to its development [see *Warnings and Precautions (5.1)*]. Advise patients to discontinue JENTADUETO XR immediately and to notify their doctor promptly if unexplained hyperventilation, malaise, myalgia, unusual somnolence, slow or irregular heartbeat, sensation of feeling cold (especially in the extremities), or other nonspecific symptoms occur. GI symptoms are common during initiation of metformin treatment and may occur during initiation of JENTADUETO XR therapy; however, advise patients to consult their doctor if they develop unexplained symptoms. Although GI symptoms that occur after stabilization are unlikely to be drug related, such an occurrence of symptoms should be evaluated to determine if it may be due to metformin-induced lactic acidosis or other serious disease.

Pancreatitis

Inform patients that acute pancreatitis has been reported during postmarketing use of linagliptin. Inform patients that persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to discontinue JENTADUETO XR promptly and contact their physician if persistent severe abdominal pain occurs [see *Warnings and Precautions (5.2)*].

Heart Failure

Inform patients of the signs and symptoms of heart failure. Before initiating JENTADUETO XR, patients should be asked about a history of heart failure or other risk factors for heart failure including moderate to severe renal impairment. Instruct patients to contact their healthcare provider as soon as possible if they experience symptoms of heart failure, including increasing shortness of breath, rapid increase in weight or swelling of the feet [see *Warnings and Precautions (5.3)*].

Monitoring of Renal Function

Inform patients about the importance of regular testing of renal function and hematological parameters when receiving treatment with JENTADUETO XR.

Instruct patients to inform their doctor that they are taking JENTADUETO XR prior to any surgical or radiological procedure, as temporary discontinuation of JENTADUETO XR may be required until renal function has been confirmed to be normal [see *Warnings and Precautions (5.1)*].

Hypoglycemia

Inform patients that the risk of hypoglycemia is increased when JENTADUETO XR is used in combination with an insulin secretagogue (e.g., sulfonylurea), and that a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia [see *Warnings and Precautions (5.4)*].

Hypersensitivity Reactions

Inform patients that serious allergic reactions, such as anaphylaxis, angioedema, and exfoliative skin conditions, have been reported during postmarketing use of linagliptin (one of the components of JENTADUETO XR). If symptoms of allergic reactions (such as rash, skin flaking or peeling, urticaria, swelling of the skin, or swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing) occur, patients must stop taking JENTADUETO XR and seek medical advice promptly [see *Warnings and Precautions (5.5)*].

Missed Dose

Instruct patients to take JENTADUETO XR only as prescribed. If a dose is missed, advise patients not to double their next dose.

Alcohol Intake

Warn patients against excessive alcohol intake, either acute or chronic, while receiving JENTADUETO XR [see *Warnings and Precautions (5.1)*].

Administration Instructions

Inform patients taking JENTADUETO XR that the tablets must be swallowed whole and never split, crushed, dissolved, or chewed and that incompletely dissolved JENTADUETO XR tablets may be eliminated in the feces. Patients should be told that, if they see tablets in feces, they should report this finding to their healthcare provider [see *Dosage and Administration (2.1)*].

Blood Glucose and A1C Monitoring

Inform patients that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and A1C levels, with a goal of decreasing these levels toward the normal range. A1C monitoring is especially useful for evaluating long-term glycemic control.

Renal Function and Other Hematologic Parameters Monitoring

Inform patients that initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (e.g., eGFR) should be performed, at least on an annual basis [see *Warnings and Precautions (5.1, 5.6)*].

Severe and Disabling Arthralgia

Inform patients that severe and disabling joint pain may occur with this class of drugs. The time to onset of symptoms can range from one day to years. Instruct patients to seek medical advice if severe joint pain occurs [see *Warnings and Precautions (5.7)*].

Bullous Pemphigoid

Inform patients that bullous pemphigoid may occur with this class of drugs. Instruct patients to seek medical advice if blisters or erosions occur [see *Warnings and Precautions (5.8)*].

Pregnancy

Inform female patients that treatment with metformin may result in an unintended pregnancy in some premenopausal anovulatory females due to its effect on ovulation [see *Use in Specific Populations (8.3)*].

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IT6354JF112019

MEDICATION GUIDE
JENTADUETO® XR (JEN ta doo e' toe XR)
(linagliptin and metformin hydrochloride extended-release)
Tablets

Read this Medication Guide carefully before you start taking JENTADUETO XR and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment. If you have any questions about JENTADUETO XR, ask your doctor or pharmacist.

What is the most important information I should know about JENTADUETO XR?

Serious side effects can happen in people taking JENTADUETO XR, including:

1. Lactic acidosis. Metformin, one of the medicines in JENTADUETO XR, can cause a rare but serious condition called lactic acidosis (a buildup of an acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital.

Call your doctor right away if you have any of the following symptoms, which could be signs of lactic acidosis:

- you feel cold in your hands or feet
- you feel dizzy or lightheaded
- you have a slow or irregular heart beat
- you feel very weak or tired
- you have unusual (not normal) muscle pain
- you have trouble breathing
- you feel sleepy or drowsy
- you have stomach pains, nausea or vomiting

Most people who have had lactic acidosis with metformin have other things that, combined with metformin, led to the lactic acidosis. Tell your doctor if you have any of the following, because you have a higher chance of getting lactic acidosis with JENTADUETO XR if you:

- have severe kidney problems or your kidneys are affected by certain x-ray tests that use injectable dye.
- have liver problems
- 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 surgery
- have a heart attack, severe infection, or stroke

The best way to keep from having a problem with lactic acidosis from metformin is to tell your doctor if you have any of the problems in the list above. Your doctor may decide to stop your JENTADUETO XR for a while if you have any of these things. JENTADUETO XR can have other serious side effects. See **"What are the possible side effects of JENTADUETO XR?"**

2. Inflammation of the pancreas (pancreatitis) which may be severe and lead to death. Certain medical problems make you more likely to get pancreatitis.

Before you start taking JENTADUETO XR, tell your doctor if you have ever had:

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

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

3. Heart failure. Heart failure means that your heart does not pump blood well enough.

Before you start taking JENTADUETO XR, tell your doctor if you have ever had heart failure or have problems with your kidneys. Contact your doctor right away if you have any of the following symptoms:

- increasing shortness of breath or trouble breathing, especially when you lie down
- swelling or fluid retention, especially in the feet, ankles or legs
- an unusually fast increase in weight
- unusual tiredness

These may be symptoms of heart failure.

What is JENTADUETO XR?

- JENTADUETO XR is a prescription medicine that contains 2 diabetes medicines, linagliptin and metformin. JENTADUETO XR can be used along with diet and exercise to lower blood sugar in adults with type 2 diabetes when treatment with both linagliptin and metformin is appropriate.
- JENTADUETO XR is not for people with type 1 diabetes.
- JENTADUETO XR is not for people with diabetic ketoacidosis (increased ketones in the blood or urine).
- If you have had pancreatitis in the past, it is not known if you have a higher chance of getting pancreatitis while you take JENTADUETO XR.

- It is not known if JENTADUETO XR is safe and effective in children under 18 years of age.

Who should not take JENTADUETO XR?

Do not take JENTADUETO XR if you:

- have severe kidney problems
- have a condition called metabolic acidosis or diabetic ketoacidosis (increased ketones in the blood or urine).
- are allergic to linagliptin, metformin, or any of the ingredients in JENTADUETO XR. See the end of this Medication Guide for a complete list of ingredients in JENTADUETO XR.

Symptoms of a serious allergic reaction to JENTADUETO XR may include:

- skin rash, itching, flaking or peeling
- raised red patches on your skin (hives)
- swelling of your face, lips, tongue and throat that may cause difficulty in breathing or swallowing
- difficulty with swallowing or breathing

If you have any of these symptoms, stop taking JENTADUETO XR and contact your doctor or go to the nearest hospital emergency room right away.

What should I tell my doctor before using JENTADUETO XR?

Before you take JENTADUETO XR, tell your doctor about all of your medical conditions, including if you:

- have or have had inflammation of your pancreas (pancreatitis).
- have severe kidney problems
- have liver problems
- have heart problems, including congestive heart failure
- drink alcohol very often, or drink a lot of alcohol in short term "binge" drinking
- are going to get an injection of dye or contrast agents for an x-ray procedure. JENTADUETO XR may need to be stopped for a short time. Talk to your doctor about when you should stop JENTADUETO XR and when you should start JENTADUETO XR again. See "**What is the most important information I should know about JENTADUETO XR?**"
- have type 1 diabetes. JENTADUETO XR should not be used to treat people with type 1 diabetes.
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if JENTADUETO XR will harm your unborn baby. If you are pregnant, talk with your doctor about the best way to control your blood sugar while you are pregnant.
- **are a premenopausal woman (before the "change of life"), who does not have periods regularly or at all.** Talk to your doctor about birth control choices while taking JENTADUETO XR if you are not planning to become pregnant since JENTADUETO XR may increase your chance of becoming pregnant. Tell your doctor right away if you become pregnant while taking JENTADUETO XR.
- are breastfeeding or plan to breastfeed. It is not known if JENTADUETO XR passes into your breast milk. Talk with your doctor about the best way to feed your baby if you take JENTADUETO XR.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. JENTADUETO XR may affect the way other medicines work, and other medicines may affect how JENTADUETO XR works.

Especially tell your doctor if you take:

- other medicines that can lower your blood sugar
- rifampin (Rifadin[®], Rimactane[®], Rifater[®], Rifamate[®])*, an antibiotic that is used to treat tuberculosis

Ask your doctor or pharmacist for a list of these medicines if you are not sure if your medicine is one that is listed above. Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I take JENTADUETO XR?

- Take JENTADUETO XR exactly as your doctor tells you to take it.
- Take JENTADUETO XR each day with a meal. Taking JENTADUETO XR with a meal may lower your chance of having an upset stomach.
- Take JENTADUETO XR 1 time each day.
- Take JENTADUETO XR tablets whole. Do not break, cut, crush, dissolve, or chew JENTADUETO XR tablets before swallowing. If you cannot swallow JENTADUETO XR tablets whole, tell your doctor.
- You may see something that looks like the JENTADUETO XR tablet in your stool (bowel movement). If you see tablets in your stool, talk to your doctor. Do not stop taking JENTADUETO XR without talking to your doctor.
- If you miss a dose, take it with food as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take 2 doses of JENTADUETO XR at the same time.
- If you take too much JENTADUETO XR, call your doctor or Poison Control Center at 1-800-222-1222 or go to the nearest hospital emergency room right away.

- Your doctor may tell you to take JENTADUETO XR along with other diabetes medicines. Low blood sugar can happen more often when JENTADUETO XR is taken with certain other diabetes medicines. See "**What are the possible side effects of JENTADUETO XR?**"
- You may need to stop taking JENTADUETO XR for a short time. Call your doctor for instructions if you:
 - are dehydrated (have lost too much body fluid). Dehydration can occur if you are sick with severe vomiting, diarrhea, or fever, or if you drink a lot less fluid than normal.
 - plan to have surgery
 - are going to get an injection of dye or contrast agent for an x-ray procedure. See "**What is the most important information I should know about JENTADUETO XR?**" and "**Who should not take JENTADUETO XR?**"
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection, or surgery, the amount of diabetes medicine that you need may change. Tell your doctor right away if you have any of these conditions and follow your doctor's instructions.
- Check your blood sugar as your doctor tells you to.
- Stay on your prescribed diet and exercise program while taking JENTADUETO XR.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.
- Your doctor will do blood tests to check how well your kidneys are working before and during your treatment with JENTADUETO XR.

What are the possible side effects of JENTADUETO XR?

JENTADUETO XR may cause serious side effects, including:

- See "**What is the most important information I should know about JENTADUETO XR?**"
- **Low blood sugar (hypoglycemia).** If you take JENTADUETO XR with another medication that can cause low blood sugar, such as sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take JENTADUETO XR. Signs and symptoms of low blood sugar may include:

○ headache	○ irritability	○ drowsiness	○ hunger	○ weakness
○ fast heart beat	○ dizziness	○ sweating	○ confusion	○ feeling jittery
- **Allergic (hypersensitivity) reactions.** Serious allergic reactions can happen after your first dose or up to 3 months after starting JENTADUETO XR. Symptoms may include:

○ swelling of your face, lips, throat, and other areas on your skin	○ difficulty with swallowing or breathing
○ raised, red areas on your skin (hives)	○ skin rash, itching, flaking, or peeling

 If you have these symptoms, stop taking JENTADUETO XR and call your doctor or go to the nearest hospital emergency room right away.
- **Joint pain.** Some people who take medicines called DPP-4 inhibitors, one of the medicines in JENTADUETO XR, may develop joint pain that can be severe. Call your doctor if you have severe joint pain.
- **Skin reaction.** Some people who take medicines called DPP-4 inhibitors, one of the medicines in JENTADUETO XR, may develop a skin reaction called bullous pemphigoid that can require treatment in a hospital. Tell your doctor right away if you develop blisters or the breakdown of the outer layer of your skin (erosion). Your doctor may tell you to stop taking JENTADUETO XR.

The most common side effects of JENTADUETO XR include stuffy or runny nose and sore throat **and** diarrhea.

These are not all the possible side effects of JENTADUETO XR. For more information, ask your doctor or pharmacist. Tell your doctor if you have any side effects that bother you or that do not go away.

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

How should I store JENTADUETO XR?

- Store JENTADUETO XR between 68°F and 77°F (20°C and 25°C).
- Keep tablets dry.

Keep JENTADUETO XR and all medicines out of the reach of children.

General information about the safe and effective use of JENTADUETO XR

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

This Medication Guide summarizes the most important information about JENTADUETO XR. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about JENTADUETO XR that is written for health professionals.

What are the ingredients in JENTADUETO XR?

Active Ingredients: linagliptin and metformin hydrochloride

Inactive Ingredients: polyethylene oxide, hypromellose, and magnesium stearate. The coating contains the following inactive ingredients: hydroxypropyl cellulose, hypromellose, talc, titanium dioxide, arginine, polyethylene glycol, ferric oxide yellow (2.5 mg/1000 mg), carnauba wax, ferrousferrous oxide, propylene glycol, and isopropyl alcohol.

What is type 2 diabetes?

Type 2 diabetes is a condition in which your body does not make enough insulin, and/or the insulin that your body produces does not work as well as it should. Your body can also make too much sugar. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems. The main goal of treating diabetes is to lower your blood sugar to a normal level. High blood sugar can be lowered by diet and exercise, and by certain medicines when necessary. Talk to your doctor about how to prevent, recognize, and take care of low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and other problems you have because of your diabetes.

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