JENTADUETO XR—linagliptin and metformin hydrochloride tablet, film coated, extended release
Boehringer Ingelheim Pharmaceuticals, Inc.

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

WARNINGS AND PRECAUTIONS

WARNING: LACTIC ACIDOSIS
- Risk factors include: history of liver disease, severe renal impairment (eGFR <30 mL/min/1.73 m²), older age, obesity, and concomitant use of drugs that increase the risk of lactic acidosis (e.g., metformin, certain antibiotics, and certain anticonvulsants). Use caution if any of these factors are present.
- Lactic acidosis is an emergency and requires immediate medical attention. If lactic acidosis is suspected, discontinue JENTADUETO XR and institute general supportive measures in a hospital setting. If lactic acidosis is confirmed, discontinue drug and institute general supportive measures in a hospital setting.
- Risk factors for lactic acidosis include renal impairment, concomitant use of certain drugs, older age (≥65 years old), metabolic acidosis, and any condition that reduces tissue perfusion (e.g., dehydration).
- Patients with chronic kidney disease, particularly those with eGFR below 30 mL/min/1.73 m², are at an increased risk of lactic acidosis.

CONTRAINDICATIONS

- Metformin hydrochloride: Hypersensitivity to any component of JENTADUETO XR.
- Linagliptin: Pregnancy and breastfeeding.
- Metformin: Hypersensitivity to metformin, diabetic ketoacidosis, severe renal impairment (eGFR <30 mL/min/1.73 m²), or lactic acidosis.
- Pancreatitis: Patients with a history of pancreatitis or who are at increased risk of developing pancreatitis.

DOSE AND ADMINISTRATION

- 5 mg linagliptin/1000 mg metformin hydrochloride extended-release tablet
- 10 mg linagliptin/1000 mg metformin hydrochloride extended-release tablet

- Initial U.S. Approval: 2012
- Full prescribing information for JENTADUETO XR available on boehringer-ingelheim.com.

ADVERSE REACTIONS

- Lactation: See boxed warning.
- Geriatric Use: Use with caution in geriatric patients, particularly those with impaired renal function.
- Pregnancy: Use only if the potential benefit justifies the potential risk to the fetus.
- Use of alternative treatments is strongly recommended.
- Alcohol can potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake.
- Carbonic anhydrase inhibitors may increase risk of lactic acidosis. Consider more frequent monitoring.
- Hypersensitivity reactions: Consider as a possible cause for unexplained joint pain and discontinue drug if appropriate.
- Arthralgia: Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for unexplained joint pain and discontinue drug if appropriate.

FDA-REPORTED ADVERSE REACTIONS

- Hypersensitivity reactions: Hypersensitivity reactions have been reported, including anaphylaxis, angioedema, and anaphylactoid reactions.
- Lactic acidosis: Risk factors include: renal impairment, concomitant use of certain drugs, older age (≥65 years old), metabolic acidosis, and any condition that reduces tissue perfusion (e.g., dehydration).
- Pancreatitis: Symptoms include abdominal pain, nausea, vomiting, and/or symptoms consistent with acute pancreatitis. Consider as a possible cause for unexplained joint pain and discontinue drug if appropriate.
- Arthralgia: Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for unexplained joint pain and discontinue drug if appropriate.

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Revised: 8/2017
JENTADUETO XR tablets are available in the following dosage forms and strengths:

JENTADUETO XR is a combination of linagliptin and extended-release metformin hydrochloride.

2.1 Recommended Dosing

Recommended starting dose:
- In patients currently not treated with metformin, initiate JENTADUETO XR treatment with 5 mg linagliptin total daily dose and a similar total daily dose of metformin 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.

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.

2.2 Recommended Dosing in Renal Impairment

Recommended starting dose:
- In patients with an eGFR between 30 and 60 mL/min/1.73 m², assess benefit 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, alcoholic liver disease, or cirrhosis, 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: white, oval-shaped coated tablets with one side printed in black ink with the Boehringer Ingelheim logo and “1000M” on the bottom line.
- 2.5 mg/1000 mg: yellow, oval-shaped coated tablets with one side printed in black ink with the Boehringer Ingelheim logos “D2” on the top line and “1000M” on the bottom line.
4 CONTRAINDICATIONS

JENTADUETO XR is contraindicated in patients with:

- Severe renal impairment (eGFR < 30 mL/min/1.73 m²) [see Warnings and Precautions (5.2)].
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin [see Warnings and Precautions (5.2)].
- A history of hypersensitivity reaction to linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity [see Warnings and Precautions (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 have had a sudden onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence. In some reports, hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis has been characterized by elevations of blood lactic acid concentrations (>5 mmol/L), or an increase in blood lactate levels (without evidence of lactic acidemia or lacticemia), and an increased lactate/pyruvate ratio; metformin plasma levels generally > 5 mg/L. 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 linagliptin-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (preferably hydrochloride is dialyzable, with clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has otherwise revealed no excess reversibility of symptom and recovery. Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur immediatly 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 specific patient’s renal function include [see Dosage and Administration (2.2), Clinical Pharmacology (12.2)]:
  - Before initiating JENTADUETO XR, obtain an estimated glomerular filtration rate (eGFR) [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 where 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 due that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation (e.g., cations drugs) [see Drug Interactions (7.3)]. 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)].

- **Rhabdomyolysis:** In patients with severe renal impairment, rhabdomyolysis has been reported in postmarketing cases. Therefore, consider more frequent monitoring of patients.

- **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 hyperperfusion and hypernatremia), cardiac collapse (shock), acute myocardial infarction, seizures, and other conditions associated with hypoxemia. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, use of JENTADUETO XR in patients with clinical or laboratory evidence of hepatic disease.

5.2 Pancreatitis

There have been reports of acute pancreatitis, including fatal cases, 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 uncompensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as SUls 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 of 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.
Angiodysplasia has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angiodysplasia to another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angiodysplasia with JENTADUETO XR.

5.6 Vitamin B<sub>12</sub> Levels

In a controlled, 28-week clinical trial of metformin decrease in serum levels of vitamin B<sub>12</sub> levels, without clinical manifestations, was observed in approximately 7% of metformin-treated patients. Such decrease, possibly due to interference with B<sub>12</sub> absorption from the B<sub>12</sub>-mimetic factor complex, is, however, rarely associated with anemia or megaloblastic manifestations due to the short duration (1-2 years) 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 B<sub>12</sub> levels appears to be rapidly reversible with discontinuation of metformin or vitamin B<sub>12</sub> 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 B<sub>12</sub> or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B<sub>12</sub> levels. In these patients, routine serum vitamin B<sub>12</sub> 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 Bulbar Pemphigoid

Postmarketing cases of bulbar 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 bulbar 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 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 1500 mg) has been evaluated in 2816 patients with type 2 diabetes mellitus treated for ≥12 weeks in clinical trials.

Three placebo-controlled studies with linagliptin + metformin were conducted: 2 studies were 24 weeks in duration, 1 study was 12 weeks in duration. In the 3 placebo-controlled clinical studies, adverse reactions which occurred in ≥5% of patients receiving linagliptin + metformin (n=875) and were more common than in patients given placebo or metformin (n=536) included nausea (5.7% vs 4.2%), flatulence, asthenia, indigestion, abdominal discomfort, and headache.

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

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

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

<table>
<thead>
<tr>
<th></th>
<th>Linagliptin n=212</th>
<th>Metformin n=212</th>
<th>Combination of Linagliptin and Metformin n=212</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (5.2)</td>
<td>10 (4.7)</td>
<td>16 (7.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (5.7)</td>
<td>5 (2.4)</td>
<td>14 (6.6)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 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.

### Metformin

Adverse reactions reported in ≥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%).

### Other Adverse Reactions

Other adverse reactions reported in ≥5% 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 (1.3% vs 0%) and hyperglycemia (2.4% vs 0%) when linagliptin was used as add-on to sulfonylurea; hyperglycemia (2.3% vs 0.8%) and weight increased (2.3% vs 0.8%) when linagliptin was used as add-on to glitazone; and nausea (2.1% vs 0%) when linagliptin was used as add-on basal insulin therapy.

### Hypoglycemia

Hypoglycemia was reported in 1.4% of 212 subjects treated with linagliptin + metformin (n=12), 14.2% of 212 subjects treated with metformin, and 1.4% of 212 subjects treated with placebo. When linagliptin was administered in combination with metformin and a sulfonylurea, 0% (0 of 72) of 212 patients reported hypoglycemia compared with 10% (13 of 72) of 203 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 Test**

### Linagliptin

**Decrease in Urine Acids:** Changes in laboratory values that occurred more frequently in the linagliptin group and ≥2% 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 increase in lipase was 2.7 times the mean lipase level compared to 2.7 times the mean lipase level in the placebo arm. Lipase levels above 3 times upper limit of normal were seen 2.2% compared to 1.7% patients in the placebo and placebo arm, respectively.

**Medication:**

Decrease in Vitamin B<sub>12</sub> Absorption: Long-term treatment with metformin has been associated with a decrease in vitamin B<sub>12</sub> absorption which may very rarely result in clinically significant vitamin B<sub>12</sub> deficiency (e.g., megaloblastic anemia) [see Warnings and Precautions (5.8)].

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 reaction including anaphylaxis, angioedema, and exfoliative skin conditions [see Warnings and Precautions (5.3)]
- Severe and disabling arthralgia [see Warnings and Precautions (5.7)]
- Bilious periphitis [see Warnings and Precautions (5.8)]
- Rash
- Mouth ulceration, stomatitis

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. Concurrent 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

Concurrent use of drugs that interfere with common renal tubular transport systems involved in the renal excretion of metformin (e.g., organic cation transporter-2 (OCT2) binding and toxic extraction [MATE1] inhibitors such as cimetidine, valproate, or disulfiram) 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 concurrent 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 combination 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

Concomitant use to produce hypoglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and insulin. When such drugs are administered to a patient receiving JENTADUETO XR, the patient should be closely observed to maintain adequate glycemic control.

7.5 Drug Interactions with Thiazolidinediones

Coadministration of thiazolidinediones with metformin may require lower doses of the thiazolidinedione or insulin to avoid hypoglycemia.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited data with JENTADUETO XR and Linagliptin in pregnant women are not sufficient to inform JENTADUETO XR-associated or linagliptin-associated risk for major birth defects and miscarriage. Published studies with metformin during pregnancy have not reported a clear association with metformin and major birth defects or miscarriage risk [see Drug Interactions (7.1)]. 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 is 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 or miscarriage; however, these studies were not designed to definitely establish the risk of 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 rhabdomyoma 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 maximum recommended clinical dose, based on exposure.

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 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 3% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.35 to 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 preponderous women. Therapy with metformin may result in oligospermia 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 renally excreted by the kidney; however, metformin is substantially excreted by the kidney [see Warnings and Precautions (5.1) and Clinical Pharmacology (12.5)].

Linagliptin
There were 4040 type 2 diabetes patients treated with linagliptin 5 mg from 15 clinical trials of linagliptin 10/5 mg (27%) patients were 65 years and over, while 135 (3%) were 75 years and over. Of these patients, 256 were enrolled in 12 double-blind placebo-controlled studies; 301 (25%) were 65 years and over, and 92 (8%) 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 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 therapies that may affect the half-life of metformin.

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 (5.1) and Warnings and Precautions (5.1) and Clinical Pharmacology (12.2)).

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 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 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 Blood Levels 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 C28H34N4O8 and the molecular weight is 472.54 g/mol. The structural formula is:

```
Linagliptin is a white to yellowish, non 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 aceton (ca. 1 mg/mL).

Metformin Hydrochloride
Metformin hydrochloride (N,N-diethylamilino-2-carboxamide: diethyl 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 C4H11N2HCl 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 6.08. The structural formula is:

```

JENTADUETO XR consist 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: Tableting 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, ferrosoferric oxide, magnesium stearate.

12. CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
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, therefore 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 mechanism of action is 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 (5.3)] and does not cause hypoglycemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

### 12.2 Pharmacokinetics

**Linagliptin**

Linagliptin binds to DPP-4 irreversibly and increases the concentration 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 10 mg (2 times the recommended dose), metformin, 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 concentration were approximately 36-fold higher than the peak concentration following a 5-mg dose.

### 12.3 Pharmacokinetics

**JENTADUETO XR**

Administration of JENTADUETO XR with a high-fat meal resulted in a 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$_{0-72}$) by approximately 54-71% relative to fasting, while C$_{max}$ is increased by 11%. Meals prolonged T$_{max}$ by approximately 3 hours.

**Absorption**

**Linagliptin**

The absolute bioavailability of linagliptin is approximately 30%. Following oral administration, plasma concentration of linagliptin decline in a biexponential manner with a long terminal half-life (100+ hours), related to the saturable binding of linagliptin 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 one 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 by 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 ± 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 30% 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 and high-fat meals increased systemic exposure (as measured by AUC) from metformin extended-release tablets by about 30% 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 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 95% at 1 nmol/L to 75% to 80% at 20 ng/mL, 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 604-708 L. Metformin is negligibly bound to plasma proteins, in contrast to SUs, which are more than 90% protein bound. Metformin penetrates 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 in a pharmacologically inactive metabolite, which shows a steady-state exposure of 13.3% relative to linagliptin.

**Metformin**

Metformin single-dose studies in normal subjects demonstrate that metformin is excreted unchanged, which indicates that metabolism represents a minor elimination pathway. A small fraction of absorbed metformin is metabolized to a pharmacologically inactive metabolite, which shows a steady-state exposure of 13.3% relative to linagliptin.

**Elimination**

Following administration of oral [¹⁴C]linagliptin dose to healthy subjects, approximately 85% of the administered radioactive 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 at steady state was approximately 70 mL/min. Metformin is negligibly bound to plasma proteins, in contrast to SUs, which are more than 90% protein bound. Metformin penetrates 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.

**Moxidectin**

Following oral administration of a 12.3 mg dose, C$_{max}$ appeared at 12.3 ± 2.2 hours and AUC$_{0-72}$ increased approximately 38-fold higher than the peak concentrations following a 5-mg dose.

**Warnings and Precautions**

**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$_{0-72}$ by 71% and C$_{max}$ by 90%) 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 3% 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)].

**Hypoglycemia**

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

**Hypoglycemia**

Linagliptin: In patients with mild hepatic impairment (Child-Pugh class A) steady-state exposure (AUC$_{0-72}$) of linagliptin was approximately 25% lower and C$_{max}$ was approximately 30% lower than in healthy subjects. In patients with moderate hepatic impairment (Child-Pugh class B), AUC$_{0-72}$ of linagliptin was about 45% lower and C$_{max}$ was approximately 40% lower than in healthy subjects. Patients with severe hepatic impairment (Child-Pugh class C) had comparable exposure of linagliptin in terms of AUC$_{0-72}$ 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 reduction in DPP-4 inhibition.

**Metformin**

Metformin hydrochloride: No pharmacokinetic studies of metformin have been conducted in patients with
**Pharmacokinetics**

Linagliptin is a P-glycoprotein (P-gp) substrate, and inhibits P-gp mediated transport of digoxin at high concentrations. 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 2J2.

Linagliptin: Race had no clinically meaningful effect on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis. Metformin hydrochloride: Neither metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes mellitus when studied 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.

**Drug Interactions**

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. Strong inducers of CYP3A4 or P-gp (e.g., rifampin) decrease exposure to linagliptin to subtherapeutic concentrations. For patients requiring use of such drugs, an alternative to linagliptin is strongly recommended. No dose adjustment of linagliptin recommended based on results of the described pharmacokinetic studies.

**Table 2 Effect of Coadministered Drugs on Systemic Exposure of Linagliptin**

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dosing of Coadministered Drug*</th>
<th>Dosing of Linagliptin*</th>
<th>Geometric Mean Ratio (ratio with/without coadministered drug)</th>
<th><strong>AUC</strong></th>
<th><strong>Cmax</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No dose adjustments required for the following coadministered drugs:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>850 mg TID</td>
<td>10 mg QD</td>
<td>1.07</td>
<td>1.02</td>
<td></td>
</tr>
<tr>
<td>Glyburide</td>
<td>1.75 mg</td>
<td>5 mg QD</td>
<td>1.02</td>
<td>1.01</td>
<td></td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>45 mg QD</td>
<td>10 mg QD</td>
<td>1.13</td>
<td>1.07</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>20 mg BID</td>
<td>5 mg</td>
<td>2.01</td>
<td>2.05</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>800 mg QD</td>
<td>7.5 mg QD</td>
<td>1.00</td>
<td>0.96</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3 Effect of Linagliptin on Systemic Exposure of Coadministered Drugs**

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dosing of Coadministered Drug*</th>
<th>Dosing of Linagliptin*</th>
<th>Geometric Mean Ratio (ratio with/without coadministered drug)</th>
<th><strong>AUC</strong></th>
<th><strong>Cmax</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No dose adjustments required for the following coadministered drugs:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>450 mg TID</td>
<td>10 mg QD</td>
<td>1.01</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>Glyburide</td>
<td>1.75 mg</td>
<td>5 mg QD</td>
<td>0.91</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>45 mg QD</td>
<td>10 mg QD</td>
<td>0.94</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>20 mg BID</td>
<td>5 mg</td>
<td>0.90</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>800 mg QD</td>
<td>7.5 mg QD</td>
<td>1.00</td>
<td>0.96</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4 Effect of Coadministered Drug on Plasma Metformin Systemic Exposure**

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dosing of Coadministered Drug*</th>
<th>Dosing of Metformin*</th>
<th>Geometric Mean Ratio (ratio with/without coadministered drug)</th>
<th><strong>AUC</strong></th>
<th><strong>Cmax</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No dose adjustments required for the following coadministered drugs:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glyburide</td>
<td>5 mg</td>
<td>500 mg QD</td>
<td></td>
<td>0.91</td>
<td>0.92</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>45 mg</td>
<td>100 mg</td>
<td></td>
<td>1.01</td>
<td>1.22</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>10 mg</td>
<td>150 mg</td>
<td></td>
<td>1.16</td>
<td>1.21</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>40 mg</td>
<td>150 mg</td>
<td></td>
<td>1.01</td>
<td>1.04</td>
</tr>
</tbody>
</table>

**Precautions**

- Hepatic impairment.
- **Studies Characterizing the Pharmacokinetics of Linagliptin and Metformin after Administration of JENTADUETO XR:**

**Pediatric**

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

**Race**

Studies 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: Neither 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).

**Notes**

- **TID = three times daily**
- **BID = twice daily**
- **QD = once daily**
- **†AUC = AUC(0 to 24 hours) for single-dose treatments and AUC = AUC(TAU) for multiple-dose treatments**
- **# Multiple dose (steady state) unless otherwise noted**
- **‡**
Drugs that are eliminated by renal tubular secretion may reduce metformin elimination; use Warnings and Precautions (5.1) and Drug Interactions (7.1).  

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dosing of Coadministered Drug*</th>
<th>Dosing of Metformin*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyburide</td>
<td>5 mg</td>
<td>500 mg</td>
</tr>
<tr>
<td></td>
<td>10 mg</td>
<td>850 mg</td>
</tr>
<tr>
<td>Furosemide</td>
<td>40 mg</td>
<td>850 mg</td>
</tr>
<tr>
<td>Hydrochloride</td>
<td>10 mg</td>
<td>850 mg</td>
</tr>
<tr>
<td>Propranolol</td>
<td>40 mg</td>
<td>850 mg</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>400 mg</td>
<td>850 mg</td>
</tr>
<tr>
<td>Metformin</td>
<td>400 mg</td>
<td>850 mg</td>
</tr>
</tbody>
</table>

Table 5 Effect of Metformin on Coadministered Drug Systemic Exposure

### 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**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Placebo</th>
<th>Linagliptin 2.5 mg</th>
<th>Metformin 500 mg</th>
<th>Linagliptin 2.5 mg + Metformin 500 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FPG (mg/dL)</strong></td>
<td>11.1</td>
<td>7.3</td>
<td>7.1</td>
<td>7.1</td>
</tr>
<tr>
<td><strong>A1C (%)</strong></td>
<td>9.0</td>
<td>7.3</td>
<td>7.1</td>
<td>7.1</td>
</tr>
<tr>
<td><strong>Change from baseline (adj. mean)</strong></td>
<td>0.1</td>
<td>-0.5</td>
<td>0.4</td>
<td>-0.5</td>
</tr>
<tr>
<td><strong>Difference from placebo</strong></td>
<td>-1.2</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td><strong>Change from baseline (adj. mean)</strong></td>
<td>0.1</td>
<td>-0.5</td>
<td>0.4</td>
<td>-0.5</td>
</tr>
<tr>
<td><strong>Difference from placebo</strong></td>
<td>-1.2</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
</tr>
</tbody>
</table>

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility JENTADUETO XR

No animal studies have been conducted with the combined product in JENTADUETO XR to evaluate carcinogenesis, mutagenesis, or impairment of fertility. General toxicity studies in each 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 males and females in a 2-year study at doses of 6, 10, and 16 mg/kg. The highest dose of 16 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 males in a 2-year study at doses up to 25 mg (male) and 20 mg (female), or approximately 35 and 27 times the clinical dose based on AUC exposure. Higher doses of linagliptin in female mice (100 mg/kg) increased the incidence of lymphomas 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 mutation assay, a chromosomal aberration test in human lymphocytes, and in an in vitro 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**

Long-term carcinogenicity studies have been performed in Sprague-Dawley rats at doses of 150, 300, and 435 mg/kg in males and 150, 450, and 900 mg/kg in females. These doses are both approximately 1.4, 4, and 8 times normal human recommended daily human dose of 2000 mg/day based on body surface area comparison. No evidence of carcinogenicity with metformin was found in either male or female rats. A carcinogenicity study was also performed in Sprague-Dawley rats 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), the chromosomal aberration test (human lymphocytes) and in vivo 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.

No animal studies have been conducted with the combined products in JENTADUETO XR to evaluate carcinogenicity, mutagenicity, or impairment of fertility.

### 14.2 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 794 patients with type 2 diabetes mellitus and inadequate glycemic control on diet and exercise participated in the 24-week, randomized, double-blind, parallel-group, randomized, 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 (≤7.0% vs >7.0%) and a prior oral antihyperglycemic drug (none vs metformin). Patients were randomized in a 2:2:2:2:2:2 ratio to either placebo or one of 5 active-treatment arms. Patients were randomized in a 1:2:2:2:2:2 ratio to either placebo or one of 5 active-treatment arms. Approximately equal numbers of patients were randomized to receive initial therapy with 5 mg of linagliptin once daily, 500 mg or 1000 mg of metformin twice daily, or 2.5 mg of linagliptin twice daily in combination with 500 mg or 1000 mg of metformin twice daily. Patients who failed to meet specific glycemic goals during the study were treated with sulfonylurea, thiazolidinedione, or insulin rescue therapy.

Initial therapy with the combination of linagliptin and metformin provided significant improvements in A1C, and fasting plasma glucose (FPG) compared to placebo, to metformin alone, and to linagliptin alone (Table 6, Figure 1). The adjusted mean treatment difference in A1C from baseline to week 24 (LOG A1C) 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; -1.3% (95% CI -1.4, -1.1, 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 1000 mg twice daily; and -0.8% (95% CI -1.0, -0.6, p < 0.0001) for linagliptin 2.5 mg/metformin 1000 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.
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 ≥8.5% to ≤12.0%) participated in a 24-week, randomized, double-blind, study designed to assess the efficacy of linagliptin in combination with metformin vs linagliptin. Patients were randomized (1:1), after a 2-week run-in period, to either linagliptin 5 mg plus metformin (1500 to 2000 mg per day, n=159) or 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 improvement 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%, -0.46%).

| Table 7 Glycemic Parameters at 24 Weeks in Study Comparing Linagliptin in Combination with Metformin to Linagliptin in Treatment-Naïve Patients* |
|---------------------|---------------------|---------------------|
| A1C (%)** | Linagliptin 5 mg + Metformin | Linagliptin 5 mg + Placebo |
| 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) | -- |
| Pattern in % achieving A1C ≤7.5%* | 82 (53.6) | 85 (59) |
| FPG (mg/dL)** | Number of patients | n=153 | n=150 |
| Baseline (mean) | 134 | 138 |
| Change from baseline (adjusted mean)** | -5.4 | -5 |
| Difference from linagliptin (adjusted mean)** (95% CI) | -1.07† (-3.1, -5.5) | -- |
| **p<0.0001 compared to linagliptin, †p=0.00005 compared to linagliptin** |

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 a run-in period of approximately 6 weeks on metformin as a dose of at least 1500 mg per day (in monotherapy). Patients who failed to meet specific glycemic goals during the studies were treated with glimepiride rescue.

In combination with metformin, linagliptin provided statistically significant improvement in A1C, FPG, and 2-hour PPG compared to placebo (Table 8). Rescue glycemic therapy was used in 1.8% of patients treated with linagliptin 5 mg and in 10.9% 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* |
|---------------------|---------------------|---------------------|
| A1C (%) | Linagliptin 5 mg + Metformin | Placebo + Metformin |
| Number of patients | n=513 | n=175 |
| Baseline (mean) | 8.1 | 8.0 |
| Change from baseline (adjusted mean)*** | -0.5 | -0.5 |
16.4 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 102 diabetic patients with suboptimal 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 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 ≥9.0% to 10.0%) were randomized 1:1 to the addition of linagliptin 5 mg once daily or glimepiride. Randomization was stratified by baseline HbA1c (≥8.5% vs <8.5%), and the previous use of antihyperglycemic drugs (metformin alone or metformin plus one other OAD). Patients receiving glimepiride were given an initial dose of 1 mg per day and then electively titrated over the next 12 weeks to a maximum dose of 4 mg per day. Patients receiving linagliptin were treated with a fixed dose of 5 mg per day. Both agents were titrated over the next 12 weeks to a maximum dose of 4 mg per day, as needed to optimize glycemic control. Therefore, the glimepiride dose was to be kept constant, except for down-titration to prevent hypoglycemia.

After 32 weeks and 104 weeks, linagliptin and glimepiride both reduced hemoglobin A1c by 0.4% for linagliptin, 0.6% for glimepiride; and 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 glimepiride. 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.

16.5 Add-On Combination Therapy with Metformin and a Sulfonylurea

A total of 1098 patients with type 2 diabetes mellitus participants 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 commonly sulfonylureas used by patients in the study were glimepiride (31%), glibenclamide (26%), and gliclazide (26% not available include United States). Patients were 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 glimepiride rescue. Glycemic end points measured included A1C and FPG.

In combination with a sulfonylurea and metformin, linagliptin provided statistically significant improvement 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 9 Glycemic Parameters at 52 and 104 Weeks in Study Comparing Linagliptin to Glimepiride as Add-On Therapy in Patients Inadequately Controlled on Metformin**

<table>
<thead>
<tr>
<th>A1C (%)</th>
<th>Week 32</th>
<th>Week 104</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Linagliptin 5 mg + Metformin</td>
<td>Glimepiride as add-on (mean ± SEM)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>764</td>
<td>755</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>7.7</td>
<td>7.7</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean***</td>
<td>-0.4</td>
<td>-0.6</td>
</tr>
<tr>
<td>Difference from baseline (adjusted mean***</td>
<td>0.2 (0.1, 0.3)</td>
<td>-0.1 (0.1, 0.1)</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>Number of patients</td>
<td>753</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>156</td>
<td>156</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean***</td>
<td>-1.5</td>
<td>-1.6</td>
</tr>
</tbody>
</table>

**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 FPG as continuous covariates. P-values for the interaction between treatment and number of prior OADs are shown.

16.6 SUPPLIED/STORAGE AND HANDLING

ENTADOTEK 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 “DS” on the top line and “1000MG” on the bottom line, are supplied as follows:

Bottles of 30 (NDC: 0079-0127-33)
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 hyperglycemia and hypoglycemia, 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 risk 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 pain occurs, especially in the abdomen, or other symptoms of lactic acidosis develop [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 (5.1)].

Hypersensitivity Reaction

Inform patients that immune-mediated reactions, such as anaphylaxis, angioedema, and exfoliative skin conditions, have been reported during postmarketing use of linagliptin. If a patient experiences a reaction, the patient should stop taking JENTADUETO XR and contact their doctor as soon as possible [see Warnings and Precautions (5.1)].

Miscellaneous

If patients develop a rash while taking JENTADUETO XR, discontinue JENTADUETO XR promptly and notify their doctor promptly if any rash occurs [see Warnings and Precautions (5.1)].

Stoppage

Inform patients that acute pancreatitis has been reported during postmarketing use of linagliptin. Inform patients that severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Inform patients to discontinue JENTADUETO XR promptly and contact their physician if persistent severe abdominal pain occurs [see Warnings and Precautions (5.1)].

Hypertension

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. Inform patients to contact their healthcare provider as soon as possible if they experience symptoms of heart failure, including increased shortness of breath, rapid increase in weight or swelling of the feet [see Warnings and Precautions (5.1)].

Monitoring of Renal Function

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

Monitoring of Hemoglobin Parameters

Inform 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)].

Monitoring of Serum Creatinine

Inform patients that the risk of hyperkalemia 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 hyperkalemia [see Warnings and Precautions (5.1)].

Hypoglycemia

Inform patients that immune-mediated reactions, such as anaphylaxis, angioedema, and exfoliative skin conditions, have been reported during postmarketing use of metformin. If a patient experiences a reaction, the patient should stop taking JENTADUETO XR and contact their doctor as soon as possible [see Warnings and Precautions (5.1)].

Hypersensitivity Reaction

Inform patients that immune-mediated reactions, such as anaphylaxis, angioedema, and exfoliative skin conditions, have been reported during postmarketing use of metformin. If a patient experiences a reaction, the patient should stop taking JENTADUETO XR and contact their doctor as soon as possible [see Warnings and Precautions (5.1)].

Miscellaneous

Inform patients that acute pancreatitis has been reported during postmarketing use of linagliptin. Inform patients that severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Inform patients to discontinue JENTADUETO XR promptly and contact their physician if persistent severe abdominal pain occurs [see Warnings and Precautions (5.1)].

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Inform 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)].

Monitoring of Serum Creatinine

Inform patients that the risk of hyperkalemia 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 hyperkalemia [see Warnings and Precautions (5.1)].
How should I take JENTADUETO XR?

Take JENTADUETO XR 1 time each day. Take JENTADUETO XR each day with a meal. Taking JENTADUETO XR with a meal may lower your chance of having an upset stomach.

When should I take it?

Take JENTADUETO XR at the same time each day. It does not matter if you take it in the morning, afternoon, or evening.

Before you start taking JENTADUETO XR:

Tell your doctor if you have ever had:
- heart problems, including congestive heart failure
- liver problems
- severe kidney problems or your kidneys are affected by certain x-ray tests that use injectable dye.
- a history of alcoholism
- a condition called metabolic acidosis or diabetic ketoacidosis (increased ketones in the blood or urine).
- a condition called lactic acidosis (a buildup of an acid in the blood) that can cause death.
- a condition called pancreatitis (inflammation of your pancreas) which may be severe and lead to death. Certain medical problems make you more likely to get pancreatitis.
- a history of gallstones, which may be severe and lead to death. Certain medical problems make you more likely to get gallstones.
- high blood triglyceride levels

Who should not take JENTADUETO XR?

Do not take 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.
- have a condition called 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 it again.
- 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.
- have type 1 diabetes.
- have a history of alcoholism.
- have had lactic acidosis. It is not known if 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.
  - got 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 work out with activity or exercise and do not drink enough fluids.
  - have surgery.
  - have a heart attack, severe infection, or injury.

Serious side effects can happen in people taking JENTADUETO XR, including:
- difficulty with swallowing or breathing
- swelling of your face, lips, tongue and throat that may cause difficulty in breathing or swallowing
- skin rash, itching, flaking or peeling
- unusual tiredness

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 levels 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).

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

Before you start taking JENTADUETO XR:

Tell your doctor if you have ever had:
- inflammation of your pancreas (pancreatitis)
- a history of alcoholism
- high blood triglyceride levels

What are the possible side effects of JENTADUETO XR?

The most common side effects of JENTADUETO XR include:

- unusual tiredness
- an unusually fast increase in weight
- swelling or fluid retention, especially in the feet, ankles or legs
- unusual tiredness

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

- difficulty with swallowing or breathing
- swelling of your face, lips, tongue and throat that may cause difficulty in breathing or swallowing
- skin rash, itching, flaking or peeling
- unusual tiredness

Who should I talk to 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 it again.

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

- JENTADUETO XR is not for people with type 1 diabetes.
- JENTADUETO XR should not be used to treat 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.

Are there any other precautions I should take while using JENTADUETO XR?

Before 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®, Rifater®), rifabutin (Mobicid®), rifapentine (Mutabon®), 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 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.
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.

What are the possible side effects of JENTADUETO XR?

JENTADUETO XR may cause serious side effects, including:

- **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
  - fast heart beat
  - irritability
  - dizziness
  - drowsiness
  - hunger
  - sweating
  - weakness
  - 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 (swelling or hives)
  - difficulty with swallowing or breathing
  - raised, red areas on your skin (blisters)
  - rash, itching, swelling, 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 reactions.** 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.

- **Allergic (hypersensitivity) reactions.** Some people who take medicines called DPP-4 inhibitors, one of the medicines in JENTADUETO XR, may develop an allergic reaction called angioedema. This reaction can be severe and can cause life-threatening breathing problems.

- **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 (swelling or hives)
  - rash, itching, swelling, flaking, or peeling

- **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 reactions.** 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.

What are the possible side effects of JENTADUETO XR included severe side effects, including:

- low blood sugar (hypoglycemia)
- allergic reactions
- joint pain
- skin reactions
- other medical problems

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, 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 in the United States to 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, ask your doctor. You can ask your pharmacist or doctor for information about JENTADUETO XR in a hurry.

The most common side effects of JENTADUETO XR include:

- low blood sugar (hypoglycemia)
- allergic reactions
- joint pain
- skin reactions
- other medical problems

What are the possible side effects of JENTADUETO XR included:

- low blood sugar (hypoglycemia)
- allergic reactions
- joint pain
- skin reactions
- other medical problems

How should I store JENTADUETO XR?

- Store JENTADUETO XR between 68°F and 77°F (20°C and 25°C).
- Keep tablets dry.
**JENTADUETO XR**
linagliptin and metformin hydrochloride tablet, film coated, extended release

**Product Information**
- **Product Type:** HUMAN PRESCRIPTION DRUG
- **Item Code (Source):** NDC:0597-0270
- **Route of Administration:** ORAL
- **Active Ingredient/Active Moiety**
  - **Ingredient Name:** Linagliptin
    - **Basis of Strength:** Linagliptin
    - **Strength:** 2.5 mg
  - **Ingredient Name:** Metformin hydrochloride
    - **Basis of Strength:** Metformin hydrochloride
    - **Strength:** 1000 mg

**Product Characteristics**
- **Color:** YELLOW
- **Shape:** OVAL
- **Size:** 19mm
- **Flavor:** Imprint Code: D2;1000M

**Packaging**
- **# Item Code:** NDC:0597-0270-12
  - **Package Description:** 1 in 1 CARTON
  - **Marketing Start Date:** 05/27/2016
- **# Item Code:** NDC:0597-0270-73
  - **Package Description:** 60 in 1 BOTTLE; Type 0: Not a Combination Product
  - **Marketing Start Date:** 05/27/2016
- **# Item Code:** NDC:0597-0270-94
  - **Package Description:** 180 in 1 BOTTLE; Type 0: Not a Combination Product
  - **Marketing Start Date:** 05/27/2016

**Marketing Information**
- **Marketing Category:** NDA
- **Application Number or Monograph Citation:** NDA208026
- **Marketing Start Date:** 05/27/2016

**Labeler**
- **Registrant:** Boehringer Ingelheim Pharmaceuticals, Inc. (603175944)
- **Establishment**
  - Name: Patheon Pharmaceuticals Inc.
    - Address: 005286822
    - Business Operations: LABEL(0597-0270, 0597-0275) , MANUFACTURE(0597-0270, 0597-0275) , PACK(0597-0275, 0597-0270) , ANALYSIS(0597-0270, 0597-0275)
  - Name: Patheon Inc.
    - Address: 240769596
    - Business Operations: ANALYSIS(0597-0270, 0597-0275)
  - Name: Sixarp, LLC
    - Address: 016329513
    - Business Operations: PACK(0597-0275, 0597-0270)