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APPLICATION NUMBER:
201281Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Jentadueto™ (linagliptin and metformin hydrochloride) tablets
Initial U.S. Approval: 2012

WARNING: RISK OF LACTIC ACIDOSIS

See full prescribing information for complete boxed warning.

- **Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as renal impairment, sepsis, dehydration, excess alcohol intake, hepatic impairment, and acute congestive heart failure. (5.1)**
- **Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate. (5.1)**
- **If acidosis is suspected, discontinue JENTADUETO and hospitalize the patient immediately (5.1)**

INDICATIONS AND USAGE

JENTADUETO 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 combination with insulin (1.2)

DOSAGE AND ADMINISTRATION

- Individualize the starting dose of JENTADUETO based on the patient's current regimen (2.1)
- The maximum recommended dose is 2.5 mg linagliptin/1000 mg metformin twice daily (2.1)
- Should be given twice daily with meals, with gradual dose escalation to reduce the gastrointestinal side effects due to metformin (2.1)

DOSAGE FORMS AND STRENGTHS

Tablets:

- 2.5 mg linagliptin/500 mg metformin hydrochloride
- 2.5 mg linagliptin/850 mg metformin hydrochloride
- 2.5 mg linagliptin/1000 mg metformin hydrochloride (3)

CONTRAINDICATIONS

- Renal impairment (4)
- Metabolic acidosis, including diabetic ketoacidosis (4)
- Hypersensitivity to linagliptin or metformin (4)

WARNINGS AND PRECAUTIONS

- Lactic acidosis: Warn against excessive alcohol use. JENTADUETO is not recommended in hepatic impairment or hypoxic states and is contraindicated in renal impairment. Ensure normal renal function before initiating and at least annually thereafter. (5.1, 5.2, 5.3, 5.6, 5.7)
- Temporarily discontinue JENTADUETO in patients undergoing radiologic studies with intravascular administration of iodinated contrast materials or any surgical procedures necessitating restricted intake of food and fluids (5.2)
- Hypoglycemia: When used with a sulfonylurea (SU), a lower dose of the SU may be required to reduce the risk of hypoglycemia (2.2, 5.4)
- Vitamin B₁₂ deficiency: Metformin may lower vitamin B₁₂ levels. Monitor hematologic parameters annually. (5.5)
- Macrovascular outcomes: No conclusive evidence of macrovascular risk reduction with JENTADUETO or any other antidiabetic drug (5.8)

ADVERSE REACTIONS

- Adverse reactions reported in ≥5% of patients treated with JENTADUETO and more commonly than in patients treated with placebo are nasopharyngitis and diarrhea (6.1)
- Hypoglycemia was more commonly reported in patients treated with the combination of JENTADUETO, and SU compared with those treated with the combination of SU and metformin (6.1)
- Pancreatitis was reported more often in patients randomized to linagliptin (1 per 538 person years versus zero in 433 person years for comparator) (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

- Cationic drugs eliminated by renal tubular secretion: May reduce metformin elimination. Use with caution. (7.1)
- P-glycoprotein/CYP3A4 inducer: The efficacy of JENTADUETO may be reduced when administered in combination (e.g., rifampin). Use of alternative treatments is strongly recommended. (7.2)

USE IN SPECIFIC POPULATIONS

- Pregnancy: There are no adequate and well-controlled studies in pregnant women. JENTADUETO tablets should be used during pregnancy only if clearly needed. (8.1)
- Nursing mothers: Caution should be exercised when JENTADUETO is administered to a nursing woman (8.3)
- Pediatric patients: Safety and effectiveness of JENTADUETO in patients below the age of 18 have not been established (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 1/2012

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF LACTIC ACIDOSIS

Lactic acidosis is a rare, but serious, complication that can occur due to metformin accumulation. The risk increases with conditions such as renal impairment, sepsis, dehydration, excess alcohol intake, hepatic impairment, and acute congestive heart failure.

The onset is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.

Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate.

If acidosis is suspected, JENTADUETO should be discontinued and the patient hospitalized immediately. [See Warnings and Precautions (5.1).]

1 INDICATIONS AND USAGE

1.1 Indication

JENTADUETO tablets are 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 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 has not been studied in combination with insulin.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The dosage of JENTADUETO should be individualized on the basis of both effectiveness and tolerability, while not exceeding the maximum recommended dose of 2.5 mg linagliptin/1000 mg metformin hydrochloride twice daily. JENTADUETO should be given twice daily with meals. Dose escalation should be gradual to reduce the gastrointestinal (GI) side effects associated with metformin use. For available dosage forms and strengths see [Dosage Forms and Strengths (3)].

Recommended starting dose:

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

No studies have been performed specifically examining the safety and efficacy of JENTADUETO in patients previously treated with other oral antihyperglycemic agents and switched to JENTADUETO. 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 Concomitant Use With Sulfonylurea

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

3 DOSAGE FORMS AND STRENGTHS

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

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

4 CONTRAINDICATIONS

JENTADUETO is contraindicated in patients with:

- Renal impairment (e.g., serum creatinine ≥ 1.5 mg/dL for men, ≥ 1.4 mg/dL for women, or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia [see Warnings and Precautions (5.1, 5.2)]
- 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 urticaria, angioedema, or bronchial hyperreactivity) or metformin [see Adverse Reactions (6.1)]

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

Metformin

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

The reported incidence of lactic acidosis in patients receiving metformin is approximately 0.03 cases/1000 patient-years, (with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple

when accompanied by hypoperfusion and hypoxemia due to unstable or acute failure, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal impairment and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in any patients unless measurement of creatinine clearance demonstrates that renal function is not reduced. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should be avoided in patients with clinical or laboratory evidence of hepatic impairment. Patients should be cautioned against excessive alcohol intake when taking metformin, since alcohol potentiates the effects of metformin on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure necessitating restricted intake of food or fluids. Use of topiramate, a carbonic anhydrase inhibitor, in epilepsy and migraine prophylaxis may cause dose-dependent metabolic acidosis and may exacerbate the risk of metformin-induced lactic acidosis [see *Drug Interactions (7.1) and Clinical Pharmacology (12.3)*].

The onset of lactic acidosis is often subtle, and accompanied by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. More severe acidosis may be associated with signs such as hypothermia, hypotension, and resistant bradyarrhythmias. Patients should be educated to recognize and promptly report these symptoms. If present, JENTADUETO should be discontinued until lactic acidosis is ruled out. Gastrointestinal symptoms, which are commonly reported during initiation of metformin therapy are less frequently observed in subjects on a chronic, stable, dose of metformin. Gastrointestinal symptoms in subjects on chronic, stable, dose of metformin could be caused by lactic acidosis or other serious disease.

To rule out lactic acidosis, serum electrolytes, ketones, blood glucose, blood pH, lactate levels, and blood metformin levels may be useful. Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis and may be due to other mechanisms, such as poorly-controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling.

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia). Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and supportive measures promptly instituted. Metformin is dialyzable (clearance of up to 170 mL/min under good hemodynamic conditions) and prompt hemodialysis is recommended to remove the accumulated metformin and correct the metabolic acidosis. Such management often results in prompt reversal of symptoms and recovery [see *Boxed Warning*].

5.2 Monitoring of Renal Function

Although linagliptin undergoes minimal renal excretion, metformin is known to be substantially excreted by the kidney. The risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Therefore, JENTADUETO is contraindicated in patients with renal impairment.

Before initiation of therapy with JENTADUETO and at least annually thereafter, renal function should be assessed and verified to be normal. In patients in whom development of renal impairment is anticipated (e.g., elderly), renal function should be assessed more frequently and JENTADUETO discontinued if evidence of renal impairment is present.

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

Use of concomitant medications that may affect renal function or metformin disposition:

Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or interfere with the disposition of metformin should be used with caution [see *Drug Interactions (7.1) and Clinical Pharmacology (12.3)*].

Radiological studies and surgical procedures:

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

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

5.3 Impaired Hepatic Function

Because impaired hepatic function has been associated with some cases of lactic acidosis with metformin therapy, JENTADUETO should generally be avoided in patients with clinical or laboratory evidence of hepatic disease [see *Warnings and Precautions (5.1)*].

5.4 Hypoglycemia

Linagliptin

Insulin secretagogues 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 may be required to reduce the risk of hypoglycemia when used in combination with JENTADUETO [see *Dosage and Administration (2.2)*].

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 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 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

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