CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

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

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

WARNING: RISK OF LACTIC ACIDOSIS

See full prescribing information for complete boxed warning.

- **Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL. (5.1)**
- **Risk factors include renal impairment, concomitant use of certain drugs, age ≥ 65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the Full Prescribing Information. (5 1)**
- **If lactic acidosis is suspected, discontinue JENTADUETO XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)**

----------INDICATIONS AND USAGE----------

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

Important limitations of use:

- Not for treatment of type 1 diabetes or diabetic ketoacidosis (1 2)
- Has not been studied in patients with a history of pancreatitis (1.2)

----------DOSAGE AND ADMINISTRATION----------

- Individualize the starting dose of JENTADUETO XR based on the patient's current regimen (2.1)
- Do not exceed a total daily dose of linagliptin 5 mg and metformin 2000 mg (2.1)
- Give once daily with a meal (2.1)
- Swallow whole; do not split, crush, dissolve, or chew (2.1)
- Prior to initiation, assess renal function with estimated glomerular filtration rate (eGFR) (2.2)
  - Do not use in patients with eGFR below 30 mL/min/1.73 m^2
  - Initiation is not recommended in patients with eGFR between 30 - 45 mL/min/1.73 m^2
  - Assess risk/benefit of continuing if eGFR falls below 45 mL/min/1.73 m^2
  - Discontinue if eGFR falls below 30 mL/min/1.73 m^2
- JENTADUETO XR may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

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

----------CONTRAINDICATIONS----------

- Severe renal impairment (eGFR below 30 mL/min/1.73 m^2) (4)
- Metabolic acidosis, including diabetic ketoacidosis (4)
- History of hypersensitivity reaction to linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity (4)
- Hypersensitivity to metformin (4)

----------WARNINGS AND PRECAUTIONS----------

- Lactic acidosis: See boxed warning (5.1)
- There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis. If pancreatitis is suspected, promptly discontinue JENTADUETO XR. (5.2)
- Hypoglycemia: When used with an insulin secretagogue (e.g., sulfonylurea (SU)) or insulin, consider lowering the dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia (5.3)
- Hypersensitivity reactions: There have been postmarketing reports of serious hypersensitivity reactions in patients treated with linagliptin (one of the components of JENTADUETO XR) including anaphylaxis, angioedema, and exfoliative skin conditions. In such cases, promptly discontinue JENTADUETO XR, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. (5.4)
- Vitamin B_{12} deficiency: Metformin may lower vitamin B_{12} levels. Monitor hematologic parameters annually. (5.5)
- Arthralgia: Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue drug if appropriate. (5.6)
- Macrovascular outcomes: No conclusive evidence of macrovascular risk reduction with JENTADUETO XR or any other antidiabetic drug (5.7)

----------ADVERSE REACTIONS----------

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

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

----------DRUG INTERACTIONS----------

- Carbonic anhydrase inhibitors may increase risk of lactic acidosis. Consider more frequent monitoring. (7.1)
- Drugs that are eliminated by renal tubular secretion (e.g., cationic drugs such as cimetidine), may increase the accumulation of metformin. Consider more frequent monitoring. (7.1)
- Alcohol can potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake. (7.1)
- Strong P-glycoprotein/CYP3A4 inducer: Efficacy may be reduced when administered in combination (e.g., rifampin). Use of alternative treatments is strongly recommended. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 5/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF LACTIC ACIDOSIS

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

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

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

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

1 INDICATIONS AND USAGE

1.1 Indication

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

1.2 Important Limitations of Use

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

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

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

Recommended starting dose:

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

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

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

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

2.2 Recommended Dosing in Renal Impairment

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

JENTADUETO XR is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2.

Initiation of JENTADUETO XR in patients with an eGFR between 30-45 mL/min/1.73 m^2 is not recommended.

In patients taking JENTADUETO XR whose eGFR later falls below 45 mL/min/1.73 m^2, assess benefit risk of continuing therapy.

Discontinue JENTADUETO XR if the patient's eGFR later falls below 30 mL/min/1.73 m^2 *[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 m^2; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart JENTADUETO XR if renal function is stable *[*see *Warnings and Precautions (5.1)]*.

3 DOSAGE FORMS AND STRENGTHS

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

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

4 CONTRAINDICATIONS

JENTADUETO XR is contraindicated in patients with:

- Severe renal impairment (eGFR below 30 mL/min/1.73 m^2) *[see Warnings and Precautions (5.1)]*
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin *[see Warnings and Precautions (5.1)]*
- A history of hypersensitivity reaction to linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity *[see Warnings and Precautions (5.4) and Adverse Reactions (6.1)]*
- Hypersensitivity to metformin

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

Metformin

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

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

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

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

Renal Impairment The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney *[see Clinical Pharmacology (12.3)]*.

- Before initiating JENTADUETO XR, obtain an estimated glomerular filtration rate (eGFR).
- JENTADUETO XR is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2. Initiation of JENTADUETO XR is not recommended in patients with eGFR between 30 – 45 mL/min/1.73 m^2.
- Obtain an eGFR at least annually in all patients taking JENTADUETO XR. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.
- In patients taking JENTADUETO XR whose eGFR later falls below 45 mL/min/1.73 m^2, assess the benefit and risk of continuing therapy *[see Dosage and Administration (2.2), Contraindications (4) and Clinical Pharmacology (12.3)]*.

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

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

Radiological Studies with Contrast Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop JENTADUETO XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m^2; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart JENTADUETO XR if renal function is stable.

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

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

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

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

DOCKET ALARM

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