

## NEW DRUG UPDATE

<b>Drug Name:</b>	linagliptin/metformin
<b>Trade Name (Manufacturer):</b>	Jentadueto™ (Boehringer Ingelheim)
<b>Form:</b>	Tablet
<b>Strength:</b>	2.5 mg/500 mg; 2.5 mg/850 mg; and 2.5 mg/1,000 mg
<b>FDA Approval:</b>	January 30, 2012
<b>Market Availability:</b>	Currently Available
<b>FDA Approval Classification:</b>	Standard review
<b>Classification:</b>	Specific Therapeutic Class (HIC3): Antihyperglycemics, DPP-4 Inhibitor and Biguanide Combination (C4F)

**Indication:**<sup>1</sup> Linagliptin/metformin (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. It is not indicated for the treatment of type 1 diabetes or diabetic ketoacidosis. Jentadueto has not been studied with insulin.

### **Contraindications/Warnings:**

Patients with a known hypersensitivity to linagliptin or metformin should not use Jentadueto.

Linagliptin/metformin carries a black box warning for the risk of lactic acidosis. Lactic acidosis can occur in patients who use Jentadueto due to an accumulation of metformin. It is fatal in approximately 50 percent of the cases. The reported incidence of lactic acidosis in patients receiving metformin is approximately 0.03 per 1000 patient years.

Linagliptin/metformin is contraindicated in patients with renal impairment, defined as serum creatine greater than or equal to 1.5 mg/dL for men and 1.4 mg/dL for women or abnormal creatine clearance, which may also occur from conditions such as cardiovascular collapse, acute myocardial infarction, and septicemia. Patients should have a baseline kidney function test prior to beginning linagliptin/metformin therapy and yearly thereafter. Patients should use caution when using other medications which may impair renal function. Radiological studies using iodinated contrast materials can alter renal function and may lead to lactic acidosis in patients using metformin. Therefore linagliptin/metformin should be temporarily discontinued prior to the procedure and withheld for 48 hours after the procedure. Linagliptin/metformin can be restarted once normal renal function has been verified. Linagliptin/metformin should be discontinued for any surgical procedure except for ones which are not associated with food and fluid restrictions and should not be restarted until normal renal function has been verified.

Patients who have hepatic impairment should use linagliptin/metformin with caution as lactic acidosis has occurred in these patients when using metformin.

Patients, who have acute or chronic metabolic acidosis, including diabetic ketoacidosis, should not use linagliptin/metformin. Patients with diabetic ketoacidosis should be treated with insulin.

Hypoglycemia may occur in patients with a decrease in caloric intake, increase in strenuous exercise, consumption of alcohol, or are concurrently taking other antidiabetic medications. Patients should avoid alcoholic intake since it has been known to potentiate the effect of metformin on lactate metabolism.

Metformin may decrease the serum levels of vitamin B-12 due to a decrease in absorption.

***Drug Interactions:***

Patients taking cationic drugs (i.e. digoxin, ranitidine, triamterene, etc) that are eliminated by renal tubular secretion should be monitored carefully and have dosages adjusted accordingly since there may be an interaction with metformin when competing for common renal tubular transport systems.

Concurrent use of carbonic anhydrase inhibitors with linagliptin/metformin should be used with caution since it could cause metabolic acidosis.

Concurrent use of linagliptin with P-glycoprotein and CYP3A4 inducers have shown to decrease a patient's exposure to linagliptin. Since linagliptin/metformin is a fixed dose of linagliptin the use of alternative treatments (not containing linagliptin) is recommended.

Patients taking linagliptin/metformin and drugs which affect glycemic control should be monitored carefully for changes in blood glucose levels.

***Common Adverse Effects:***

The most common adverse events which occurred in five percent or more of patients receiving linagliptin plus metformin were nasopharyngitis (6.3 percent) and diarrhea (6.3 percent). Other adverse reactions reported during concurrent use of linagliptin and metformin included urticaria, angioedema, bronchial hyperactivity, cough, decreased appetite, nausea, vomiting, pruritus, hypoglycemia and pancreatitis.

***Special Populations:***

*Pediatrics:* The safety and effectiveness of linagliptin/metformin in pediatric patients has not been established.

*Pregnancy:* Pregnancy Category B.

*Geriatrics:* Linagliptin/metformin should be used with caution in the geriatric population. Jentaduetto should not be started in patients 80 years and older unless normal renal function has been determined.

*Renal Impairment:* Linagliptin/metformin has not been studied in the renally impaired. It is contraindicated in patients with renal impairment due to the metformin component. Renal impairment has been defined as serum creatine greater than or equal to 1.5 mg/dL for men and 1.4 mg/dL for women or abnormal creatine clearance.

*Hepatic Impairment:* Linagliptin/metformin has not been studied in the hepatically impaired. The use of metformin in patients with hepatic impairment has resulted in lactic acidosis and therefore the use of Jentaduetto is not recommended.

***Dosages:***

The recommended starting dose for patients not already taking metformin is 2.5 mg linagliptin/500 mg metformin twice daily with meals. In patients already taking metformin the recommended starting dose is 2.5 mg linagliptin and the patient's current dose of metformin taken at each of the two daily meals. The maximum recommended dose of 2.5 mg linagliptin/1000 mg metformin twice daily should not be exceeded. The dose should have a gradual increase in order to minimize any gastrointestinal side effects from metformin. Patients

who are already taking both single entity products concurrently may be switched to linagliptin/metformin (Jentadueto) containing the same doses of each drug. If the patient is also taking an insulin secretagogue a lower dose of the insulin secretagogue may be needed to prevent hypoglycemia. No studies have been performed examining the safety and efficacy of switching patients from other oral hypoglycemics to linagliptin/metformin therefore increased monitoring is warranted during transition.

**Clinical Trials:** A literature search was performed using “Jentadueto” and “metformin and linagliptin”. Placebo-controlled trials were included in the absence of comparative trials.

There have been no clinical efficacy studies performed with linagliptin/metformin (Jentadueto). However, coadministration of the single entity medications has been studied in type 2 diabetes mellitus patients who were not well controlled in their diet and exercise and in combination with a sulfonylurea. The bioequivalence of Jentadueto to linagliptin and metformin administered together as single entities was demonstrated in healthy subjects.

A 24 week randomized, double-blinded, placebo-controlled factorial study involving 791 patients was performed to determine the efficacy of linagliptin as initial therapy with metformin.<sup>2</sup> Patients (52 percent) entering the study already on antihyperglycemic therapy went through a four week wash out period followed by a two week placebo run-in period. Patients who had inadequate glycemic control (HbA1c greater than or equal to seven percent and less and or equal to 10.5 percent) were randomized into the study. Forty-eight percent of patients entering the study were not taking an antihyperglycemic and went straight into the two week placebo run-in phase. Patients who had inadequate glycemic control (HbA1c greater than or equal to 7.5 percent and less 11 percent) after the two week placebo run-in phase were randomized into the study. Randomization was stratified by baseline HbA1c (less than 8.5 percent versus greater than or equal to 8.5 percent) and prior use of an antihyperglycemic medication. Patients were randomized in a 1:2:2:2:2 ratio to either placebo or one of the five treatment arms (linagliptin 5 mg once daily; metformin 500 mg twice daily; linagliptin 2.5 mg twice daily plus metformin 500 mg twice daily; metformin 1000 mg twice daily; and linagliptin 2.5 mg twice daily plus metformin 1000 mg twice daily). Initial therapy with the combination of linagliptin and metformin significantly improved HbA1c levels (change from baseline of -1.2 for linagliptin 2.5 mg/metformin 500 mg twice daily and -1.6 for linagliptin 2.5 mg/metformin 1000 mg twice daily) compared to linagliptin monotherapy (change from baseline of -0.5), metformin monotherapy (change from baseline of -0.6 for metformin 500 mg twice daily and -1.1 for metformin 1000 mg twice daily), and placebo (change from baseline of 0.1), CI= 95 percent. The fasting plasma glucose also improved with linagliptin plus metformin (change from baseline of -33 for linagliptin 2.5 mg/metformin 500 mg twice daily and -49 for linagliptin 2.5 mg/metformin 1000 mg twice daily) compared to linagliptin monotherapy (change from baseline of -9), metformin monotherapy (change from baseline of -16 for metformin 500 mg twice daily and -32 for metformin 1000 mg twice daily), and placebo (change from baseline of 10), CI= 95 percent and p<0.0001.

A 24 week, double-blinded, randomized, placebo-controlled study was performed in 701 patients with type 2 diabetes to test the efficacy of adding linagliptin to metformin.<sup>3,4</sup> There were 491 patients taking metformin greater than or equal to 1500 mg per day who entered the study after a two week run-in period with placebo. There were 207 patients taking metformin plus another oral antihyperglycemic who entered the study after stopping the other oral antihyperglycemic and performing a run-in phase with metformin monotherapy of at least 1500 mg per day. Patients were then randomized to the addition of linagliptin 5 mg or placebo once

daily. If necessary, rescue glimepiride was administered to patients with poor glycemic control. When comparing the linagliptin plus metformin group to the placebo plus metformin group statistically significant improvements were seen in AHb<sub>1</sub>C (-0.5 versus 0.15), fasting plasma glucose (-11 and 11), and 2-hour postprandial glucose levels (-49 versus 18) for those treated with linagliptin (CI 95%). Rescue glimepiride therapy was needed in 7.8 percent of patients using linagliptin plus metformin versus 18.9 percent using placebo plus metformin (CI 95%). Overall, 28.3 percent of the linagliptin plus metformin group and 11.4 percent of the placebo plus metformin group reached an HbA<sub>1c</sub> goal of less than seven percent (CI 95%).

A 104 week double-blinded, glimepiride-controlled, non-inferiority study was performed in patients with type 2 diabetes with insufficient glycemic control despite being on metformin compared to patients having coadministration of linagliptin plus metformin.<sup>5</sup> Patients on metformin monotherapy had a run-in period of two weeks and patients taking metformin with another oral antihyperglycemic had a metformin monotherapy (daily dose at least 1,500 mg) run-in period of six weeks and washout of the other antihyperglycemic agent. After an additional two week placebo run-in period patients with poor glycemic control (HbA<sub>1c</sub> 6.5 to 10 percent) were randomized 1:1 to the addition of linagliptin 5 mg daily (n=766) or glimepiride (n=761, initial dose 1 mg per day and titrated up to 4 mg per day as needed over 12 weeks). After 52 weeks both groups, linagliptin plus met form and glimepiride plus met form, saw a decrease in HbA<sub>1c</sub> and fasting plasma glucose levels, -0.4 and -0.6 (CI 97.5 percent) and -9 and -16, respectively. The incidence of hypoglycemia was lower in the linagliptin plus metformin group compared to the glimepiride plus metformin group, 5.4 and 31.8 percent, respectively (p< 0.0001). Patients treated with linagliptin plus metformin experienced a significant decrease from baseline body weight compared to a significant weight gain in the glimepiride plus metformin group (-1.1 kg versus +1.4 kg, p<0.0001).

A 24 week, randomized, double-blinded, placebo controlled study was performed in 1058 patients with type 2 diabetes to assess the efficacy of linagliptin in combination with metformin and a sulfonylurea. Patients were randomized to receive linagliptin 5 mg (n=778) or placebo (n=262) once daily. Pioglitazone was used as a rescue medication for those patients having poor glycemic control. The study determined that linagliptin provided statistically significant improvements in HbA<sub>1c</sub> and fasting plasma glucose levels. Patients treated with linagliptin plus metformin and a sulfonylurea had a reduction in HbA<sub>1c</sub> and fasting plasma glucose levels, -0.7 and -5, respectively, and patients using placebo plus metformin and a sulfonylurea had a reduction of -0.1 in HbA<sub>1c</sub> levels but an increase of 8 in fasting plasma glucose levels (CI 95%). Rescue therapy was needed in 5.4 percent of patients treated in the linagliptin group versus 13 percent in the placebo group. Overall 31.2 percent of the linagliptin plus metformin and sulfonylurea patients and 9.2 percent of the placebo plus metformin and sulfonylurea patients reached a goal HbA<sub>1c</sub> level of less than seven percent.<sup>6</sup>

**Other Drugs Used for Condition:**<sup>7</sup> Patients and prescribers have many options available when selecting an oral antihyperglycemic medication such as: alpha-glucosidase inhibitors: acarbose (Precose<sup>®</sup>) miglitol (Glyset<sup>®</sup>); biguanides/metformin (Fortamet<sup>®</sup>, Glucophage/XR<sup>®</sup>, Glumetza<sup>™</sup>, metformin/XR, Riomet<sup>®</sup>); DPP-4 inhibitors: sitagliptin (Januvia<sup>™</sup>), saxagliptin (Onglyza<sup>™</sup>), linagliptin (Tradjenta<sup>™</sup>); meglitinides: repaglinide (Prandin<sup>™</sup>), nateglinide (Starlix<sup>®</sup>); sulfonylureas: glimepiride (Amaryl<sup>®</sup>), chlorpropamide, glyburide (Glynase<sup>®</sup>, Diabeta<sup>®</sup>), glimepiride, glipizide/XL, glipizide/XL (Glucotrol/XL<sup>®</sup>), tolazamide, tolbutamide; and thiazolidinediones: pioglitazone (Actos<sup>™</sup>) and rosiglitazone (Avandia<sup>®</sup>). Several multi-strength combination products are also available. Specifically the combinations of biguanide/DPP-4

inhibitors are: sitagliptin/metformin immediate-release (IR) (Janumet) sitagliptin/metformin extended-release (ER) (Janumet™ XR) and saxagliptin/metformin ER (Kombiglyze™ XR).

**Place in Therapy:** Linagliptin/metformin (Jentadueto) offers a fixed dose combination of linagliptin and IR metformin in adults with type 2 diabetes. Single ingredients of this product are available as linagliptin (Tradjenta) and metformin. The combination tablet offers the convenience of a single tablet and potential increase in compliance. Currently three additional biguanide/DPP-4 combination products are available: sitagliptin/metformin IR (Janumet), sitagliptin/metformin ER (Janumet XR), and saxagliptin/metformin ER (Kombiglyze XR).

**Suggested Utilization Management:**

<b>Anticipated Therapeutic Class Review (TCR) Placement</b>	Hypoglycemics, Incretin Mimetics/Enhancers
<b>Clinical Edit</b>	Prior authorization if the product is determined to be non-preferred. Trial and failure of a preferred product. Trial and failure of metformin. Deny if patient has diagnosis of type 1 diabetes
<b>Quantity Limit</b>	2 tablets/day; 60 tablets per 30 days
<b>Duration of Approval</b>	One year
<b>Drug to Disease Hard Edit</b>	Type 2 diabetes
<b>Retro-DUR</b>	Yes
<b>Provider Profiling</b>	No

**References**

<sup>1</sup> Jentadueto [package insert]. Ridgefield, CT; Boehringer Ingelheim Pharmaceuticals; January 2012.  
<sup>2</sup> Jentadueto [package insert]. Ridgefield, CT; Boehringer Ingelheim Pharmaceuticals; January 2012.  
<sup>3</sup> Jentadueto [package insert]. Ridgefield, CT; Boehringer Ingelheim Pharmaceuticals; January 2012.  
<sup>4</sup> Taskinen M., Rosenstock J., Tamminen I., et al. Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: a randomized, double-blinded, placebo-controlled study. *Diabetes, Obesity and Metabolism*. 2010; (13):65-74.  
<sup>5</sup> Jentadueto [package insert]. Ridgefield, CT; Boehringer Ingelheim Pharmaceuticals; January 2012.  
<sup>6</sup> Jentadueto [package insert]. Ridgefield, CT; Boehringer Ingelheim Pharmaceuticals; January 2012.  
<sup>7</sup> Available at: [www.clinicalpharmacology.com](http://www.clinicalpharmacology.com). Accessed February 10, 2012.