

PRODUCT BULLETIN

This material was prepared by HMP Communications, LLC in collaboration with and with funding from Boehringer Ingelheim Pharmaceuticals, Inc. and Lilly USA, LLC.

November 2011

Tradjenta[™]
(linagliptin) tablets 5mg

TRADJENTA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. TRADJENTA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. TRADJENTA has not been studied in combination with insulin.¹

OVERVIEW OF DIABETES

Recent projections from the Centers for Disease Control and Prevention indicate that if current trends continue, the prevalence of diagnosed diabetes is likely to rise dramatically over the coming decades, more than doubling to 55.5 million adults aged 18 to 79 years by 2030 and increasing to 86.6 million adults by 2050, which is 4 times the current prevalence of 21 million diagnosed adults.² Assuming an adult population of 306 million and an undiagnosed diabetic population of 13.7 million in 2050, as many as 1 in 3 adults in the United States will have diabetes by mid-century.² In adults, type 2 diabetes accounts for approximately 90% to 95% of all diagnosed cases of diabetes.³

Among US residents aged 65 years and older, 10.9 million (26.9%) had diabetes in 2010.³ Diabetes in older adults is on the rise. Data from 2007 show that 23.1% of people aged 60 and older, and 25% of nursing home residents met the diagnostic criteria for diabetes (mainly type 2 diabetes).⁴ It has been suggested that the prevalence of diabetes in nursing facilities may be underestimated.⁵

Individuals with type 2 diabetes face an increased risk of hyperglycemia and hypoglycemia. Preventing hyperglycemia and hypoglycemia are both important components of diabetes management. The American Diabetes Association (ADA) has recommended setting goals for glycemic control in people with diabetes focusing on glyated hemoglobin (A1C), fasting plasma glucose (FPG), and postprandial glucose (PPG). The ADA has recommended goals for A1C (<7%), FPG (70-130 mg/dL), and PPG (<180 mg/dL).⁶ Glycemic goals should be individualized based on duration of diabetes, age and life expectancy, comorbid conditions, hypoglycemia unawareness, and individual patient considerations.⁶

Diabetes also presents economic challenges. On average, people diagnosed with diabetes have medical expenditures that are approximately 2.3 times higher than those without diabetes.³ In 2007, the

annual estimated cost of managing diagnosed diabetes in the United States was \$174 billion, of which excess medical expenditures and reduced national productivity accounted for \$116 billion and \$58 billion, respectively.⁷ The estimated costs for approximately 6.3 million people living in the United States who had undiagnosed diabetes in 2007 were \$18 billion.⁸ Beyond the direct costs associated with diabetes are the indirect costs for such factors as increased absenteeism and reduced productivity for both employed and unemployed individuals and lost productive capacity due to early mortality.⁷

According to the American Medical Directors Association, diabetes care accounts for an estimated 32% of Medicare expenses. The estimated cost of providing care in long-term care facilities for residents with diabetes increased from \$13.9 billion in 2002 to \$18.5 billion in 2007.⁵

TRADJENTA AS A TREATMENT OPTION FOR TYPE 2 DIABETES

TRADJENTA is the only dipeptidyl peptidase-4 (DPP-4) inhibitor FDA approved at 1 dose for adult patients with type 2 diabetes as an adjunct to diet and exercise to improve glycemic control, representing another treatment option for the management of type 2 diabetes.¹

TRADJENTA is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide. Thus, TRADJENTA 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. TRADJENTA binds to DPP-4 in a reversible manner, binds selectively to the active site of the DPP-4 enzyme, and selectively inhibits DPP-4 but not DPP-8 or DPP-9 activity in vitro at concentrations approximating therapeutic exposures.¹

The pharmacokinetics of TRADJENTA has been characterized in healthy individuals and people with type 2 diabetes. After oral administration of a single 5-mg dose to healthy participants, TRADJENTA was rapidly absorbed with T_{max} occurring 1.5 hours post-dose. The effective half-life accumulation of TRADJENTA, as determined from oral administration of multiple doses of TRADJENTA 5 mg, is approximately 12 hours.¹ Following oral administration, the majority (about 90%) of TRADJENTA is excreted unchanged, indicating that metabolism represents a minor elimination pathway. Approximately 85% of TRADJENTA was eliminated via the enterohepatic system

Please see Important Safety Information on page 4 and accompanying full Prescribing Information, including Patient Information.

(80%) or urine (5%) within 4 days of dosing.¹

EFFICACY AND SAFETY OF TRADJENTA™ (linagliptin) TABLETS

In patients with type 2 diabetes, treatment with TRADJENTA produced clinically significant improvements in A1C and FPG, and 2-hour PPG in certain subsets of patients, compared with placebo.^{1,9-12}

TRADJENTA AS A MONOTHERAPY

A total of 730 patients with type 2 diabetes participated in 2 double-blind, placebo-controlled studies of 18- and 24-week duration to evaluate the efficacy and safety of TRADJENTA monotherapy.^{1,9} In both monotherapy studies, patients currently on an oral antidiabetic drug (OAD) discontinued the drug and underwent a diet, exercise, and drug washout period of about 6 weeks that included an open-label placebo run-in phase during the last 2 weeks. Participants with inadequate glycemic control (A1C, 7%-10%) after the washout period were randomized; participants not currently taking an OAD (off therapy for at least 8 weeks) with inadequate glycemic control (A1C, 7%-10%) were randomized after completing the 2-week open-label placebo run-in period.^{1,9}

In the 18-week study, only patients ineligible for metformin therapy were recruited. In this study, 76 patients were randomized to placebo and 151 to TRADJENTA 5 mg.¹ In the 24-week study, 167 participants were randomized to placebo and 336 to TRADJENTA 5 mg.^{1,9} Two-hour PPG was assessed in a subset of patients in the 24-week study only.⁹

Treatment with TRADJENTA 5 mg daily provided significant improvements in A1C and FPG, and also in 2-hour PPG in the 24-week study, compared with placebo.^{1,9} In the 18-week study, 12% of patients receiving TRADJENTA 5 mg and 18% who received placebo required rescue therapy with pioglitazone and/or insulin. In the 24-week study, 10.2% of patients receiving TRADJENTA 5 mg and 20.9% of patients receiving placebo required rescue therapy with metformin.^{1,9}

As is typical for trials of agents to treat type 2 diabetes, the mean reduction in A1C with TRADJENTA appears to be related to the degree of A1C elevation at baseline.^{13,14} In these 18- and 24-week studies, the changes from baseline in A1C were -0.4% and -0.4%, respectively, for those given TRADJENTA, and 0.1% and 0.3%, respectively, for those given placebo.^{1,9} In both studies, the adjusted mean change from baseline in FPG were -13.3 mg/dL and -8.5 mg/dL, respectively, for those given TRADJENTA, and 7.2 mg/dL and 14.8 mg/dL, respectively, for those given placebo.^{1,9} In the 24-week study, the adjusted mean change from baseline 2-hour PPG was -33.5 mg/dL for TRADJENTA and 24.9 mg/dL for placebo.^{1,9}

TRADJENTA AS AN ADD-ON THERAPY

TRADJENTA has been studied in combination with metformin, pioglitazone, and sulfonylurea therapy.

Patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study to assess the efficacy of

TRADJENTA in combination with metformin. Patients already on metformin at a dose of ≥ 1500 mg per day (or maximum tolerated dose) were randomized after completing a 2-week, open-label, placebo run-in period. Patients on metformin and another OAD were randomized after a run-in period of approximately 6 weeks on metformin (at a dose of ≥ 1500 mg per day or maximum tolerated dose) in monotherapy.^{1,10} After a second assessment for patient eligibility was conducted, 700 patients were randomized to receive TRADJENTA 5 mg plus metformin (continued at their usual dosage throughout the study, n=523) or placebo plus metformin (continued at their usual dosage throughout the study, n=177) once daily for 24 weeks. Glimepiride rescue therapy was used in 7.8% of patients treated with TRADJENTA 5 mg and in 18.9% of patients treated with placebo.^{1,10}

Study results showed significant improvements in A1C, FPG, and 2-hour PPG in the TRADJENTA plus metformin group, compared with placebo. At week 24, the adjusted mean change in A1C from baseline for TRADJENTA was -0.5% and 0.15% for placebo.^{1,10} The adjusted mean change in FPG from baseline for TRADJENTA was -10.7 mg/dL, compared with 10.5 mg/dL for placebo. For the TRADJENTA group, the adjusted mean change from baseline 2-hour PPG was -48.9 mg/dL and 18.3 mg/dL for the placebo group.^{1,10}

In a separate 24-week, randomized, double-blind, placebo-controlled study, the efficacy of TRADJENTA in initial combination with pioglitazone was assessed.^{1,11} Therapy was stopped in patients on OAD therapy for a period of 6 weeks (4-week wash-out followed by a 2-week, open-label, placebo run-in period). Drug-naïve patients entered directly into the 2-week, placebo run-in period. After the run-in period, 389 patients were randomized to receive either TRADJENTA 5 mg (n=259) or placebo (n=130), both in addition to pioglitazone 30 mg daily. Glycemic endpoints measured were A1C and FPG.^{1,11}

In initial combination with pioglitazone 30 mg, TRADJENTA 5 mg provided significant improvements in the adjusted mean change in A1C and FPG compared to placebo with pioglitazone (-1.1% vs -0.6% for A1C, respectively, and -32.6 mg/dL vs -18.4 mg/dL for FPG, respectively). Metformin rescue therapy was used in 7.9% of patients treated with TRADJENTA 5 mg/pioglitazone 30 mg and 14.1% of patients treated with placebo/pioglitazone 30 mg. Patient weight increased in both groups during the study with an adjusted mean change from baseline of 2.3 kg and 1.2 kg in the TRADJENTA 5-mg/pioglitazone 30-mg and placebo/pioglitazone 30-mg groups, respectively ($P=0.014$).^{1,11}

The efficacy of TRADJENTA was also assessed in combination with a sulfonylurea and metformin in a 24-week, randomized, double-blind, placebo-controlled study of 1058 patients with type 2 diabetes. The most commonly used sulfonylureas were glimepiride (31%), glibenclamide (26%), and gliclazide (26%, not available in the United States). Participants receiving a sulfonylurea and metformin were randomized to receive TRADJENTA 5 mg or placebo, each administered once daily. Pioglitazone rescue therapy was used in 5.4% of patients treated with TRADJENTA 5 mg and in 13% of patients

treated with placebo. Glycemic endpoints included A1C and FPG.^{1,12}

In combination with a sulfonylurea and metformin, TRADJENTA™ (linagliptin) tablets 5 mg provided significant improvements in A1C and FPG, compared with placebo. In the entire study population (patients on TRADJENTA in combination with a sulfonylurea and metformin), a mean reduction from baseline relative to placebo in A1C of -0.6% and in FPG of -12.7 mg/dL was observed.^{1,12}

A total of 245 patients with type 2 diabetes participated in an 18-week, randomized, double-blind, placebo-controlled study that evaluated the efficacy of TRADJENTA in combination with a sulfonylurea. Patients on sulfonylurea monotherapy (n=142) were randomized after completing a 2-week single-blind placebo run-in period. Patients on a sulfonylurea plus 1 OAD (n=103) were randomized after a washout period of 4 weeks and a 2-week single-blind placebo run-in period. Participants were then randomized to receive TRADJENTA 5 mg plus a sulfonylurea (n=161) or to placebo plus a sulfonylurea (n=84), each administered once daily.^{1,15} Glycemic endpoints measured included A1C and FPG.¹

In combination with a sulfonylurea, TRADJENTA provided significant improvements in A1C, compared with placebo following 18 weeks of treatment (-0.5% vs -0.1%, respectively); the improvements in FPG observed with TRADJENTA were not statistically significant when compared with placebo.¹ Rescue therapy was used in 7.6% of patients treated with TRADJENTA 5 mg and 15.9% of patients treated with placebo.^{1,15}

The efficacy of TRADJENTA is being evaluated in a 104-week double-blind, glimepiride-controlled, noninferiority study in patients with type 2 diabetes and insufficient glycemic control despite metformin therapy. Patients being treated with metformin only entered a run-in period of 2 weeks, whereas patients pretreated with metformin and 1 additional OAD entered a run-in treatment period of 6 weeks with metformin monotherapy (dose of ≥1500 mg per day) and washout of the other agent.¹ After an additional 2-week placebo run-in period, those with inadequate glycemic control (A1C, 6.5%–10%) were randomized 1:1 to the addition of TRADJENTA 5 mg

once daily or glimepiride. 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 as needed to optimize glycemic control. Thereafter, the glimepiride dose was to be kept constant, except for down-titration to prevent hypoglycemia.¹

After 52 weeks (interim analysis), TRADJENTA and glimepiride had similar mean reductions from baseline in A1C in the intent-to-treat population using last observation carried forward analysis (-0.4% vs -0.6%, respectively) from a baseline mean of 7.7%. These results were consistent with the completers analysis. Patients receiving TRADJENTA also experienced a significant ($P<0.0001$) mean decrease from baseline body weight, compared with a significant weight gain in participants receiving glimepiride (-1.1 kg vs +1.4 kg).¹

ADVERSE REACTIONS

The safety of TRADJENTA has been demonstrated in >4000 patients with type 2 diabetes in clinical trials.¹ Adverse reactions that occurred in ≥5% receiving TRADJENTA and more commonly than in patients given placebo included nasopharyngitis (5.8% vs 5.5%). Adverse reactions reported in ≥2% treated with TRADJENTA 5 mg daily as monotherapy or in combination with pioglitazone, sulfonylurea, or metformin and at least 2-fold more commonly than in patients treated are shown in the Table. Other adverse reactions reported in clinical studies with TRADJENTA were hypersensitivity and myalgia.¹

In the placebo-controlled studies, 195 (7.6%) of the total 2566 patients treated with TRADJENTA 5 mg reported hypoglycemia compared to 49 patients (4.1%) of 1183 placebo-treated patients. The incidence of hypoglycemia was similar to placebo when TRADJENTA were administered as monotherapy or in combination with metformin or with pioglitazone. Hypoglycemia was more commonly reported in patients treated with the combination of TRADJENTA and sulfonylurea, compared with those treated with the combination of placebo and sulfonylurea.¹

Table. Adverse Reactions Reported in ≥2% of Patients Treated with TRADJENTA and at Least 2-Fold Greater Than with Placebo in Placebo-Controlled Clinical Studies of TRADJENTA Monotherapy or Combination Therapy

	Monotherapy,* n (%)		Combination with Metformin,† n (%)		Combination with SU, n (%)		Combination with Metformin + SU, n (%)		Combination with Pioglitazone, n (%)	
	TRADJENTA n=765	Placebo n=458	TRADJENTA n=590	Placebo n=248	TRADJENTA n=161	Placebo n=84	TRADJENTA n=791	Placebo n=263	TRADJENTA n=259	Placebo n=130
Nasopharyngitis	—	—	—	—	7 (4.3)	1 (1.2)	—	—	—	—
Hyperlipidemia	—	—	—	—	—	—	—	—	7 (2.7)	1 (0.8)
Cough	—	—	—	—	—	—	19 (2.4)	3 (1.1)	—	—
Hypertriglyceridemia‡	—	—	—	—	4 (2.4)	0 (0.0)	—	—	—	—
Weight increase	—	—	—	—	—	—	—	—	6 (2.3)	1 (0.8)

Note: 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.

SU = sulfonylurea. *Pooled data from 7 studies; †Pooled data from 2 studies; ‡Includes reports of hypertriglyceridemia (n = 2; 1.2%) and blood triglycerides increased (n = 2; 1.2%).

Please see Important Safety Information on page 4 and accompanying full Prescribing Information, including Patient Information.

TRADJENTA™ (linagliptin) TABLETS DOSING AND ADMINISTRATION

The recommended dose of TRADJENTA is 5 mg once daily. TRADJENTA can be taken with or without food. No dose adjustment is recommended for patients with renal impairment or for patients with hepatic impairment. When TRADJENTA is used in combination with an insulin secretagogue (eg, sulfonylurea), a lower dose of insulin secretagogue may be required to reduce the risk of hypoglycemia.¹

TRADJENTA IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

TRADJENTA is contraindicated in patients with a history of hypersensitivity reaction to linagliptin, such as urticaria, angioedema or bronchial hyperreactivity.

WARNINGS AND PRECAUTIONS

Use with Medications Known to Cause Hypoglycemia

Insulin secretagogues (e.g., sulfonylurea) are known to cause hypoglycemia. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with TRADJENTA.

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with TRADJENTA or any other antidiabetic drug.

ADVERSE REACTIONS

Adverse reactions reported in $\geq 5\%$ of patients treated with TRADJENTA and more commonly than in patients treated with placebo included nasopharyngitis.

Hypoglycemia was more commonly reported in patients treated with the combination of TRADJENTA and sulfonylurea compared with those treated with the combination of placebo and sulfonylurea.

Pancreatitis was reported more often in patients randomized to linagliptin (1 per 538 person-years versus zero in 433 person-years for comparator).

DRUG INTERACTIONS

The efficacy of TRADJENTA may be reduced when administered in combination with a strong P-glycoprotein or CYP3A4 inducer

(e.g., rifampin). Therefore, use of alternative treatments is strongly recommended.

USE IN SPECIFIC POPULATIONS

There are no adequate and well-controlled studies in pregnant women. Therefore, TRADJENTA should be used during pregnancy only if clearly needed.

It is not known whether linagliptin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRADJENTA is administered to a nursing woman.

Safety and effectiveness of TRADJENTA in patients below the age of 18 have not been established. ■

REFERENCES

1. Tradjenta (linagliptin) tablets [package insert]. Ridgefield, CT: Boehringer Ingelheim International GmbH; 2011.
2. Boyle JP, Thompson TJ, Gregg EW, et al. Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and pre-diabetes prevalence. *Popul Health Metr.* 2010;8:29.
3. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, 2011. www.cdc.gov/diabetes/pubs/pdf/nfds_2011.pdf. Accessed August 2, 2011.
4. Pandya N, Nathanson E. Managing diabetes in long-term care facilities: benefits of switching from human insulin to insulin analogs. *J Am Med Dir Assoc.* 2010; 11(3):171-178.
5. American Medical Directors Association. *Diabetes Management in the Long-Term Care Setting: Clinical Practice Guideline.* Columbia, MD: AMDA; 2008, revised 2010.
6. American Diabetes Association: standards of medical care in diabetes [position statement]. *Diabetes Care.* 2011;34(Suppl 1):S11-S61.
7. American Diabetes Association. Economic costs of diabetes in the U.S. in 2007. *Diabetes Care.* 2008;31(3):596-615.
8. Zhang Y, Dall TM, Mann SE, et al. The economic costs of undiagnosed diabetes. *Popul Health Manag.* 2009;12(2):95-101.
9. Del Prato S, Barnett AH, Huisman H, et al. Effect of linagliptin monotherapy on glycaemic control and markers of cell function in patients with inadequately controlled type 2 diabetes: a randomised controlled trial. *Diabetes Obes Metab.* 2011; 13(3):258-267.
10. Taskinen MR, 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 blind, placebo controlled study. *Diabetes Obes Metab.* 2011;13(1):65-74.
11. Gomis R, Espadero RM, Jones R, et al. Efficacy and safety of initial combination therapy with linagliptin and pioglitazone in patients with inadequately controlled type 2 diabetes: a randomized, double blind, placebo controlled study. *Diabetes Obes Metab.* 2011;13(7):653-661.
12. Owens DR, Swallow R, Woerle HJ, et al. Linagliptin improves glycemic control in type 2 diabetes patients inadequately controlled by metformin and sulfonylurea without weight gain and low risk of hypoglycemia. Presented at: 70th American Diabetes Association Scientific Sessions; June 25-29, 2010; Orlando, FL. Abstract 548-P.
13. Bloomgarden ZT, Dodis R, Viscoli CM, et al. Lower baseline glycemia reduces apparent oral agent glucose-lowering efficacy: a meta-regression analysis. *Diabetes Care.* 2006;29(9):2137-2139.
14. Sherifali D, Nerenberg K, Pullenayegum E, et al. The effect of oral antidiabetic agents on A1C levels: a systematic review and meta-analysis. *Diabetes Care.* 2010; 33(8):1859-1864.
15. Lewin AJ, Arvay L, Liu D, et al. Safety and efficacy of linagliptin as add on therapy to a sulphonylurea in inadequately controlled type 2 diabetes. *Diabetologia.* 2010; 53(Suppl 1):S326.



Please click here for full Prescribing Information, including Patient Information. For more information, please visit www.tradjenta.com.

Publisher's Note: The opinions of this publication are those of the author and are not attributable to the publishers or the editors of *Annals of Long-Term Care*® or *First Report - Managed Care*. Furthermore, this publication is not intended to serve as an endorsement of the product by the publishers or the editors of *Annals of Long-Term Care*® or *First Report - Managed Care*. Clinical judgment must guide each professional in weighing the benefits of treatment against the risks. Consult product description information before prescribing.