Clinical Review of Tradjenta® (linagliptin) Tablets for Adults with Type 2 Diabetes

By John A. Welz, MPH

Tradjenta® (linagliptin) tablets contain the active ingredient linagliptin, an orally active inhibitor of the dipeptidyl peptidase (DPP)-4 enzyme.1 TRADJENTA has a mechanism of action that works in 2 ways to improve glycemic control. By increasing concentrations of the active incretin hormones glucagon-like peptide-1 and glucose-dependent insulino-tropic polypeptide, TRADJENTA stimulates the release of insulin in a glucose-dependent manner and decreases the levels of glucagon in the circulation, thereby helping to regulate glucose homeostasis.1

TRADJENTA tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. TRADJENTA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, because this medication would not be effective in these settings. TRADJENTA has not been studied in patients with a history of pancreatitis. TRADJENTA may be used in combination with insulin and other oral antihyperglycemic drugs.1

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

Significant, Placebo-Adjusted Differences in A1C Levels with TRADJENTA as Monotherapy, Dual Therapy, and Triple Therapy

TRADJENTA has been studied as monotherapy and in combination with metformin, metformin plus a sulfonulary, pioglitazone, and insulin. More than 3600 patients with type 2 diabetes were exposed to linagliptin in 10 randomized, placebo-controlled efficacy studies that evaluated the effects of linagliptin...
Figure 1. Placebo-Adjusted Difference in A1C with Oral Mono-, Dual, and Triple Therapy of Tradjenta® (linagliptin) Tablets at 24 Weeks

<table>
<thead>
<tr>
<th>Treatment</th>
<th>A1C Decrease</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRADJENTA monotherapy</td>
<td>-0.7%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline A1C 8.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRADJENTA add-on to metformin</td>
<td>-0.6%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline A1C 8.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRADJENTA add-on to metformin + SU</td>
<td>-0.6%</td>
<td></td>
</tr>
<tr>
<td>Baseline A1C 8.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRADJENTA add-on to basal insulin</td>
<td>-0.7%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline A1C 8.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRADJENTA initial combination with pioglitazone</td>
<td>-0.5%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline A1C 8.6%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

See Indication, Limitations of Use, and Important Safety Information for TRADJENTA on Page 7, and see accompanying full Prescribing Information including Medication Guide.
on glycemic control. As shown in Figure 1 (page 2), patients achieved significant, clinically meaningful differences in hemoglobin A1C levels with Tradjenta® (linagliptin) tablets monotherapy, dual therapy, and triple therapy.¹ ²

TRADJENTA monotherapy was evaluated in a phase 3, randomized, multicenter, double-blind, placebo-controlled, parallel-group study of treatment-naïve and treatment-experienced adult patients with type 2 diabetes (aged 18-80 years) who were randomized to TRADJENTA once daily (N = 336) or to placebo (N = 167) for 24 weeks.² In this study, the primary endpoint was change in A1C at 24 weeks; secondary endpoints included change from baseline in fasting plasma glucose (FGP) and in 2-hour postprandial glucose (PPG).³ At 24 weeks, the adjusted mean change in A1C from baseline was −0.4% among TRADJENTA-treated patients versus 0.3% in placebo-treated individuals, representing a significant, placebo-adjusted improvement in mean A1C of −0.7% (P <0.0001).¹ ²

Overall, 20.9% of patients in the placebo arm required the use of rescue therapy compared with 10.2% of those in the TRADJENTA arm.²

TRADJENTA as dual therapy was evaluated in a randomized, double-blind, placebo-controlled, parallel-group study of adult patients with type 2 diabetes and inadequate glycemic control who were randomized to TRADJENTA 5 mg once daily (N = 524) or to placebo (N = 177) in combination with metformin ≥1500 mg daily for 24 weeks.¹ The primary endpoint was change from baseline in A1C at study endpoint; the secondary endpoints included change from baseline in FPG and 2-hour PPG.³ The adjusted mean change from baseline in A1C was −0.5% among TRADJENTA-treated patients versus 0.15% in placebo-treated patients, representing a significant, placebo-adjusted improvement in mean A1C of −0.6% (P <0.0001) at 24 weeks of treatment.¹ ³

Overall, 18.9% of patients in the placebo arm required the use of rescue medication versus 7.8% of patients in the TRADJENTA arm.³

TRADJENTA was also studied in combination with basal insulin in adult patients with type 2 diabetes and insufficient glycemic control. In this study, a total of 1261 patients were randomized and treated with either linagliptin 5 mg once daily (N = 631) or placebo (N = 630), both in addition to existing basal insulin with or without metformin and/or pioglitazone for 24 weeks.³ Patients who failed to meet specific glycemic goals during the studies were treated with metformin rescue. Rescue therapy was used in 38.2% of patients in the TRADJENTA group and in 50.4% of those in the placebo group.³

The primary endpoint of the study was defined as change from baseline A1C, and

| Table 1. Adverse Reactions Reported in ≥2% of Adult Patients Receiving Tradjenta® (linagliptin) Tablets and More than Placebo in Placebo-Controlled Clinical Trials of TRADJENTA Monotherapy or Combination Therapy |
|-------------------------|-------------------------|-------------------------|
| Adverse reaction       | TRADJENTA 5 mg (N = 3625), N (%) | Placebo (N = 2176), N (%) |
|                        | Nasopharyngitis          | 254 (7.0)                | 132 (6.1)                      |
|                        | Diarrhea                 | 119 (3.3)                | 65 (3.0)                      |
|                        | Cough                    | 76 (2.1)                 | 30 (1.4)                      |

Source: Reference 1.

Please see Indication, Limitations of Use, and Important Safety Information for TRADJENTA on Page 7, and see accompanying full Prescribing Information including Medication Guide.

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the secondary endpoints included change from baseline in FPG after 24 weeks of treatment. At week 24, the adjusted mean change in A1C from baseline in the linagliptin-plus-basal-insulin group was –0.6% compared with 0.1% in the placebo group, representing a significant, placebo-adjusted improvement in mean A1C of –0.7% (P < 0.0001). In patients receiving Tradjenta® (linagliptin) tablets as add-on therapy to a stable dose of insulin, severe hypoglycemic events for up to 52 weeks were reported in 11 (1.7%) patients compared with 7 (1.1%) for placebo.

The use of TRADJENTA as part of a triple-therapy regimen was evaluated in a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in adult patients with type 2 diabetes and inadequate glycemic control despite treatment with metformin plus a sulfonylurea. Patients were randomized to TRADJENTA daily (N = 793) or placebo (N = 265) as an add-on to existing metformin plus sulfonylurea therapy. The primary endpoint was the change from baseline in A1C at 24 weeks.

In this study, the use of TRADJENTA resulted in significant improvements in A1C compared with placebo. The adjusted mean change in A1C levels from baseline was –0.7% in the linagliptin-plus-metformin-plus-sulfonylurea group versus –0.1% in the placebo-plus-metformin-plus-sulfonylurea group, representing a significant, placebo-adjusted improvement in mean A1C of –0.6% (P < 0.0001) at 24 weeks. A total of 13% of patients in the placebo group required the use of rescue therapy compared with 5.4% of patients in the TRADJENTA group. Insulin secretagogues and insulin are known to cause hypoglycemia. The use of TRADJENTA in combination with an insulin secretagogue (e.g., sulfonylurea) was associated with a higher rate of hypoglycemia compared with placebo in a clinical trial. Therefore, a lower dose of the insulin secretagogue or insulin may

**Figure 2. Prespecified Subgroup Analysis: Placebo-Adjusted Difference in A1C with Tradjenta® (linagliptin) Tablets at Week 24 Across All Age Groups Studied**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Baseline A1C</th>
<th>Adjusted Mean Change in A1C</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤50 years</td>
<td>8.2%</td>
<td>–0.6%</td>
</tr>
<tr>
<td>51-64 years</td>
<td>8.2%</td>
<td>–0.6%</td>
</tr>
<tr>
<td>65-74 years</td>
<td>8.1%</td>
<td>–0.6%</td>
</tr>
<tr>
<td>≥75 years</td>
<td>8.0%</td>
<td>–0.8%</td>
</tr>
</tbody>
</table>

Model includes baseline A1C, washout, treatment, study, body mass index, subgroup, and treatment-by-subgroup interaction. Full analysis set (intention-to-treat), last observation carried forward.

**Figure 3. Efficacy in African American Patients: Adjusted Mean Change in A1C from Baseline at 24 Weeks**

- Patients had to be treatment-naive or receiving a maximum of 1 oral antihyperglycemic drug (OAD) and have A1C ≥7.5% and ≤11.0% at screening. Patients who were on an antihyperglycemic drug were required to have a stable regimen with no changes for ≥10 weeks before screening. There was no washout of antihyperglycemic drug, and the drug was to be continued at the same dose throughout the trial. 15.5% of patients in the placebo group required use of rescue therapy versus 8.2% of patients in the TRADJENTA group.

- Model includes baseline A1C, washout, treatment, study, body mass index, subgroup, and treatment-by-subgroup interaction. Full analysis set (intention-to-treat), last observation carried forward.

- Source: Reference 5.
be required to reduce the risk of hypoglycemia when used in combination with Tradjenta® (linagliptin) tablets.

**Significant, Placebo-Adjusted Difference in FPG and 2-Hour PPG with TRADJENTA at 24 Weeks**

When TRADJENTA was administered as monotherapy or as add-on to metformin therapy, patients experienced significant improvements in FPG and 2-hour PPG.

With TRADJENTA monotherapy, the adjusted mean decrease from baseline in FPG was 9 mg/dL compared with a 15-mg/dL mean increase with placebo, representing a statistically significant, placebo-adjusted difference of –23 mg/dL (P <0.0001) at 24 weeks (placebo-adjusted mean; full analysis set, last observation carried forward [LOCF] of treatment). The adjusted mean decrease from baseline in 2-hour PPG was 34 mg/dL compared with a 25-mg/dL mean increase with placebo, yielding a significant, placebo-adjusted difference of –58 mg/dL (P <0.0001) at 24 weeks of treatment.

Patients receiving TRADJENTA as add-on to metformin therapy achieved an adjusted mean decrease from baseline FPG of 11 mg/dL compared with an 11-mg/dL mean increase with placebo, representing a significant, placebo-adjusted mean change of –21 mg/dL (P <0.0001) at 24 weeks of treatment. The adjusted mean decrease from baseline in 2-hour PPG was 49 mg/dL compared with an 18-mg/dL mean increase with placebo, yielding a significant, placebo-adjusted difference of –67 mg/dL (P <0.0001) at 24 weeks of treatment.

**Significant A1C Reductions Across All Age Groups Studied**

In a prespecified subgroup analysis of pooled data from the 4 pivotal phase 3 trials, adult patients with type 2 diabetes across a broad range of ages achieved significant reductions in A1C. Figure 2 shows the placebo-adjusted differences in patient A1C levels at week 24 for 4 age groups: ≤50 years, 51 to 64 years, 65 to 74 years, and ≥75 years.

Because these studies had a similar design and duration, as well as comparable eligibility criteria, the data were pooled to provide supportive evidence of efficacy and to outline the basis for the evaluation of efficacy in subgroups. Clinical experience with Tradjenta® (linagliptin) tablets has not identified differences in response between the elderly and younger patients; however, greater sensitivity to this medication in some older patients cannot be ruled out.

**TRADJENTA: Efficacy in African American Patients**

In the first study evaluating the safety and efficacy of a DPP-4 inhibitor exclusively in African American patients with type 2 diabetes, researchers reported a placebo-adjusted difference in A1C of 0.58% with TRADJENTA in African American patients at 24 weeks.

As shown in Figure 3, in a double-blind study of TRADJENTA 5 mg daily versus placebo as monotherapy or an add-on to preexisting antihyperglycemic therapy, patients experienced a 0.54% adjusted mean decrease from baseline of 8.6% with TRADJENTA (N = 93) and a 0.25% adjusted mean decrease from baseline of 8.7% with placebo (N = 105).

In this study, 27% (N = 97) of patients receiving TRADJENTA achieved an A1C goal of <7% compared with 8% (N = 108) of those receiving placebo. At week 24, there was no difference between the treatment groups in mean change from baseline for body weight. These results are consistent with those observed in previous studies with

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**Figure 4. Noninferiority Study: 104-Week Head-to-Head Study of Tradjenta® (linagliptin) Tablets versus Glimepiride in Patients Receiving Metformin (Per-Protocol Analysis)**

![Figure 4. Noninferiority Study: 104-Week Head-to-Head Study of Tradjenta® (linagliptin) Tablets versus Glimepiride in Patients Receiving Metformin (Per-Protocol Analysis)](attachment:image)

Model includes treatment, baseline A1C, and number of previous oral antihyperglycemic drugs; 24% of patients in the linagliptin group required use of rescue therapy versus 21.5% of patients in the glimepiride group.

Primary analysis: full analysis set, last observation carried forward (LOCF); linagliptin (N = 764); glimepiride (N = 755). Per-protocol analysis: completers, observed cases; linagliptin (N = 377); glimepiride (N = 387). SE indicates standard error.

Source: Reference 5.
linagliptin in other patient populations.5

The most common adverse reactions were hyperglycemia (2.8% vs 9.2%) and nasopharyngitis (3.8% vs 5.0%) for Tradjenta® (linagliptin) tablets and placebo, respectively.5

Active-Controlled Trial of Linagliptin versus Glimepiride in Combination with Metformin

The efficacy of linagliptin was evaluated in a 104-week, double-blind, glimepiride-controlled, noninferiority study in patients with type 2 diabetes and inadequate glycemic control despite metformin therapy. Patients were randomized to the addition of TRADJENTA 5 mg daily (N = 777) or to glimepiride (N = 775).5 Patients receiving glimepiride were given an initial dose of 1 mg daily, with the dosage electively titrated to a maximum of 4 mg daily, over 12 weeks. The average dose of glimepiride used in this trial was 3 mg daily.

The primary endpoint in this analysis was the change from baseline in A1C levels after 52 weeks and 104 weeks of treatment.5

As illustrated in Figure 4, after 104 weeks, patients in the full analysis set, LOCF population (N = 764) achieved an adjusted reduction in mean A1C from baseline of 0.2% at 104 weeks versus 0.4% with glimepiride (N = 755). The mean treatment difference between the groups was 0.2% (97.5% confidence interval, 0.1-0.3). Therefore, the noninferiority of linagliptin to glimepiride was demonstrated (1-sided P value = 0.0004) based on a prespecified noninferiority margin of 0.35%.5,5

Overall, 24.7% of patients in the TRADJENTA arm required the use of rescue therapy compared with 21.5% of those in the glimepiride group.5 A conclusion in favor of the noninferiority of TRADJENTA to glimepiride may be limited to patients with baseline A1C comparable to those included in the study (66% of patients had baseline A1C <8% and 91% had baseline A1C <9%).5

TRADJENTA demonstrated comparable efficacy to a sulfonylurea, with lower rates of hypoglycemia and comparative weight difference.1 In the treated set of patients, the incidence of hypoglycemia was almost 5 times lower among patients receiving TRADJENTA versus those receiving glimepiride (7.5% vs 36.1%, respectively; P <0.0001).5

In addition, the adjusted mean change in body weight from baseline over 104 weeks revealed that patients in the glimepiride arm gained an average of 2.8 lb (1.3 kg) whereas those in the TRADJENTA arm lost an average of 3.1 lb (1.4 kg) after 104 weeks of treatment.5 In this analysis, the model included continuous baseline A1C, baseline weight, number of oral antihyperglycemic agents, and treatment.5

Adverse reactions reported in ≥5% of patients treated with linagliptin and more frequently than in patients treated with glimepiride were back pain (9.1% vs 8.4%), arthralgia (8.1% vs 6.1%), upper respiratory tract infection (8.0% vs 7.6%), headache (6.4% vs 5.2%), cough (6.1% vs 4.9%), and pain in extremity (5.3% vs 3.9%).5

TRADJENTA Dosage and Administration

TRADJENTA is a single-strength DPP-4 inhibitor that is available in a 5-mg dose administered once daily for the treatment of adults with type 2 diabetes.5 Among many considerations when treating patients with type 2 diabetes, 40% of individuals with type 2 diabetes have some degree of renal impairment.7 With TRADJENTA, no dose adjustment is required, regardless of declining renal function or hepatic impairment.5 Patients with type 2 diabetes are at risk for declining renal function.8 Linagliptin, the active ingredient in TRADJENTA, has a primarily nonrenal route of excretion. The dominant excretion pathway, via the bile and gut, accounts for 80% of the oral dose in healthy individuals, whereas renal excretion accounts for 5% of the administered dose, within 4 days of dosing.1

Conclusion

TRADJENTA tablets are effective in adult patients with type 2 diabetes and inadequate glycemic control.1 In monotherapy, dual therapy, and triple therapy, patients receiving TRADJENTA achieved statistically significant reductions in A1C.1,4 As monotherapy, or in combination with other antihyperglycemic agents, TRADJENTA demonstrated significant, placebo-adjusted A1C reductions across all age groups studied.5 Furthermore, TRADJENTA demonstrated efficacy in African American patients.5

TRADJENTA has a demonstrated safety profile that has been evaluated in more than 6000 patients.1 TRADJENTA is a single-strength DPP-4 inhibitor, and no dose adjustment is required, regardless of declining renal function or hepatic impairment.1

References

Tradjenta® (linagliptin) tablets
Indication, Limitations of Use and Important Safety Information

Indication and Important Limitations of Use
TRADJENTA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. TRADJENTA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. TRADJENTA has not been studied in patients with a history of pancreatitis.

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
Pancreatitis
There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis, in patients taking TRADJENTA. Take careful notice of potential signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue TRADJENTA 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 TRADJENTA.

Use with Medications Known to Cause Hypoglycemia
Insulin secretagogues and insulin are known to cause hypoglycemia. The use of TRADJENTA in combination with an insulin secretagogue (e.g., sulfonylurea) was associated with a higher rate of hypoglycemia compared with placebo in a clinical trial. Therefore, a lower dose of the insulin secretagogue or insulin 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 ≥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. When TRADJENTA was administered in combination with metformin and a sulfonylurea, 181 of 792 (22.9%) patients reported hypoglycemia compared with 39 of 263 (14.8%) patients administered placebo in combination with metformin and a sulfonylurea. In patients receiving TRADJENTA as add-on therapy to a stable dose of insulin severe hypoglycemic events were reported in 11 (1.7%) patients compared with 7 (1.1%) for placebo.

In the clinical trial program, pancreatitis was reported in 15.2 cases per 10,000 patient-years of exposure while being treated with TRADJENTA compared with 3.7 cases per 10,000 patient-years of exposure while being treated with comparator (placebo and active comparator, sulfonylurea). Three additional cases of pancreatitis were reported following the last administered dose of linagliptin.

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 to TRADJENTA 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.

The safety and effectiveness of TRADJENTA in patients below the age of 18 have not been established.

See accompanying full Prescribing Information for TRADJENTA including Medication Guide.
About the Author

John A. Welz, MPH, is a medical and managed care writer. With more than 12 years of agency-based consulting and health plan experience, Mr Welz has expertise in strategic and tactical planning, formulary dossier development, and pharmacoeconomic modeling.

In his previous role as a member of the Health Informatics team at HIP Health Plan of New York (now EmblemHealth), Mr Welz designed and implemented quality improvement initiatives to support health plan accreditation efforts, directed drug utilization experience analyses, and conducted health outcomes studies.

Mr Welz has presented original research on smoking cessation, diabetes, and hypertension at national healthcare meetings, and is a member of the American Public Health Association.

Disclosure Statement

John A. Welz, MPH, received fair market value compensation for taking part in this activity.

Mission Statement

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This publication further provides benefit design decision makers the integrated industry information they require to devise formularies and benefit designs that stand up to today’s special healthcare delivery and business needs.

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Contact Information: For subscription information and editorial queries, please contact: editorial@engagehc.com; tel: 732-992-1892; fax: 732-992-1881.