Early type 2 diabetes is characterized by impaired insulin action known as insulin resistance, which is manifested by overproduction of glucose as the ability of insulin to suppress hepatic glucose production is reduced. As the need for insulin increases, insulin production by the pancreas is impaired, and pancreatic beta-cell mass and function decline and worsen progressively. When combined with an excessive rate of hepatic glucose production and a decrease in glucose uptake in the muscle, the progressive decline in insulin secretion leads to hyperglycemia.

The gastrointestinal tract has recently been implicated in the pathogenesis of type 2 diabetes, with the recognition that the insulin secretory response is greater to oral glucose than it is to intravenously administered glucose (called the “incretin effect”). Incretins are gut hormones that promote glucose homeostasis through the glucose-dependent regulation of insulin and glucagon. The gut hormone glucagon-like peptide-1 (GLP-1) is released in response to an ingested meal and glucose load, which stimulates insulin secretion. The release of GLP-1 is deficient in type 2 diabetes, which contributes to the development of impaired insulin secretion. The incretin effect is therefore reduced in patients with type 2 diabetes.

The Burden of Type 2 Diabetes

The prevalence of type 2 diabetes continues to increase. Approximately 26 million Americans have type 1 and type 2 diabetes, with type 2 diabetes accounting for 90% to 95% of the cases. In the pooled 2003-2006 National Health and Nutrition Examination Surveys, the national prevalence of diabetes among US adults aged ≥30 years was 13.7% for men and 11.7% for women.

The incidence of type 2 diabetes in children and adolescents is increasing among American youth. The SEARCH for Diabetes in Youth study documented that the prevalence of type 2 diabetes in the American population under age 20 years increased from 2.9 per 10,000 persons to 3.6 per 10,000 persons, a 21% increase between 2001 and 2009.

Premature mortality, which is frequently caused by cardiovascular disease (CVD), is a consequence of type 2 diabetes, especially when the disease is poorly controlled. Cardiovascular (CV) mortality increases as levels of hemoglobin (Hb)A<sub>1c</sub> rise. In addition to increasing the risk for macrovascular complications, poor glucose control is also a major risk factor for microvascular disease. Microvascular complications of type 2 diabetes and of hyperglycemia include retinal, renal, and neuropathic diseases.

HbA<sub>1c</sub> Target Levels

A 2012 position statement issued jointly by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommends an HbA<sub>1c</sub> target of <7% when instituting antihyperglycemic therapy, but individualization of treatment targets is deemed important. The HbA<sub>1c</sub> target levels are lower for younger, healthier patients (target, 6.0%-6.5%) than they are for older patients, who have comorbidities and may be prone to hypoglycemia (target, 7.5%-8.0%). Therapy should be selected and titrated to avoid hypoglycemia.

Pharmacologic Treatment Options for Type 2 Diabetes

Metformin

Metformin (Glucophage) is the first-line oral antihyperglycemic agent for most patients with type 2 diabetes who cannot achieve glycemic control through diet and lifestyle interventions. Metformin is a biguanide that reduces hepatic glucose production; its predominant mechanism of action is to achieve glycemic control. The drug is weight-neutral and does not increase the risk of hypoglycemia.

The 2012 ADA/EASD position statement supports the recommendation of metformin as the preferred initial antihyperglycemic therapy. Type 2 diabetes is a progressive disease; therefore, metformin alone often eventually fails to provide adequate glycemic control. However, there are few data to guide therapy after treatment with metformin. Advancing to combination therapy with 1 or 2 additional oral or injectable agents is reasonable if a 3-month trial of monotherapy does not maintain an HbA<sub>1c</sub> target level. Initial dual-combination therapy can be considered when HbA<sub>1c</sub> levels are ≥9%.

Jentadueto: A New Oral Antihyperglycemic Combination Therapy for Patients with Type 2 Diabetes

By Wayne Kuznar, Medical Writer
Oral therapies other than metformin include sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, meglitinides, bromocriptine, GLP-1 receptor agonists, and dipeptidyl peptidase (DPP)-4 inhibitors.

**DPP-4 Inhibitors**

DPP-4 inhibitors increase the levels of endogenous GLP-1 by 3- to 4-fold within 5 minutes of oral administration, improve glucose tolerance, and enhance pancreatic insulin secretion. These agents are weight-neutral and have a low propensity for severe hypoglycemia, which makes them an attractive add-on therapy to metformin for patients with type 2 diabetes.

Because patients with type 2 diabetes are at a high risk for CVD, the therapeutic choice should take CV risk potential into consideration. Preliminary reports show an improvement in CV risk with DPP-4 inhibitors, although clinical outcomes data are few. The results of a recent meta-analysis showed a relative risk of 0.48 for any adverse CV event and a relative risk of 0.40 for non-fatal myocardial infarction or acute coronary syndrome when managing type 2 diabetes with a DPP-4 inhibitor compared with other oral antidiabetes drugs.8 The analysis included 18 trials with 4998 patients who received DPP-4 inhibitors and 3546 patients who received comparative oral antidiabetes drugs.8 The risk for adverse CV events was not significantly different with DPP-4 inhibitors compared with placebo; however, when compared with metformin and other oral agents (ie, sulfonylureas and thiazolidinediones), the risk was lower by a significant 58% with DPP-4 inhibitor therapy.8

**FDA Approves Jentadueto Combination Tablets**

In January 2012, the US Food and Drug Administration (FDA) approved the new oral tablet Jentadueto (linagliptin and metformin hydrochloride; Boehringer Ingelheim/Lilly), which is a combination of linagliptin (Tradjenta) and metformin hydrochloride, for use with diet and exercise to improve glycemic control in adult patients with type 2 diabetes when treatment with both linagliptin and metformin is appropriate.9

**Dosing and Schedule**

Linagliptin plus metformin hydrochloride combination is available in the following strengths:

- 2.5-mg linagliptin plus 500-mg metformin hydrochloride
- 2.5-mg linagliptin plus 850-mg metformin hydrochloride
- 2.5-mg linagliptin plus 1000-mg metformin hydrochloride

The dosage of linagliptin plus metformin hydrochloride should be individualized based on effectiveness and tolerability, and should not exceed the maximum recommended dosage of 2.5-mg linagliptin plus 1000-mg metformin hydrochloride twice daily.

The recommended starting dose is 2.5-mg linagliptin plus 500-mg metformin hydrochloride twice daily for patients who are currently not receiving metformin, and 2.5-mg linagliptin and the current dose of metformin taken at each of 2 daily meals for patients who are already receiving metformin. Patients who are already receiving linagliptin and metformin as individual tablets may be switched to the combination tablet that contains the same doses of each component.9

**Clinical Pharmacology of Linagliptin plus Metformin**

**Mechanism of Action**

Linagliptin inhibits the enzyme DPP-4 to prevent the inactivation of the incretin hormones GLP-1 and glucose-dependent insulino tropic peptide (GIP). By doing so, linagliptin increases the concentrations of GLP-1 and GIP, which are involved in the physiologic regulation of glucose homeostasis. Preventing the inactivation of GLP-1 through selective inhibition of DPP-4 increases plasma insulin in response to meals.9

**Pharmacodynamics and Pharmacokinetics**

Linagliptin binds selectively to DPP-4 in a reversible manner, thereby increasing the concentrations of incretin hormones. Linagliptin increases insulin secretion and lowers glucagon secretion in a glucose-dependent manner, resulting in better regulation of glucose homeostasis.9

In healthy individuals, peak plasma concentrations occurred at approximately 1.5 hours after the administration of a 5-mg dose of linagliptin; the mean plasma area under the curve (AUC) was 139 nmol*h/L, and the maximum concentration (Cmax) was 8.9 nmol/L. The effective half-life for the accumulation of oral linagliptin, as determined from the administration of multiple 5-mg doses, is approximately 12 hours. After once-daily dosing, steady-state plasma concentrations of linagliptin were reached by the third dose, and the Cmax and the plasma AUC increased by a factor of 1.3 at steady state compared with the first dose. Plasma AUC of linagliptin increased in a less-than-dose-proportional manner in the dose range of 1 to 10 mg. The pharmacokinetics of linagliptin is similar in patients with type 2 diabetes.9

The results of a bioequivalence study in healthy individuals demonstrated that the combination tablets of linagliptin plus metformin hydrochloride at doses of 2.5 mg plus 500 mg, 2.5 mg plus 850 mg, and 2.5 mg plus 1000 mg, respectively, are bioequivalent to coadministration of corresponding doses of linagliptin and metformin as individual tablets.9
Phase 3 Clinical Trials

The safety and efficacy of concomitantly administered linagliptin, 5 mg daily, and metformin, mean daily dose of approximately 1800 mg, has been evaluated in patients with type 2 diabetes that is inadequately controlled with diet and exercise. Four placebo-controlled studies of linagliptin in combination with metformin were conducted, including (1) as initial combination therapy, (2) as linagliptin added on to metformin, (3) an active-controlled study versus glimepiride in combination with metformin, and (4) add-on combination therapy with metformin and a sulfonylurea.9

Initial Combination Therapy Trial

In a 24-week, placebo-controlled factorial study, 791 patients with type 2 diabetes (who had not been treated previously or who had received antihyperglycemic therapy) and had inadequate glycemic control with diet and exercise were randomized in a double-blind fashion to 1 of 6 arms as initial therapy: placebo, linagliptin 5 mg once daily as monotherapy, metformin 500 mg twice daily as monotherapy, linagliptin 2.5 mg twice daily plus metformin 500 mg twice daily, metformin 1000 mg twice daily as monotherapy, or linagliptin 2.5 mg twice daily plus metformin 1000 mg twice daily (Table 1).10

Linagliptin as Add-On to Metformin Study

In a 24-week, double-blind, placebo-controlled study, 701 patients who were receiving metformin ≥1500 mg daily were randomized to the addition of linagliptin 5 mg once daily or to placebo after completing a 2-week, open-label, placebo run-in period.11 Patients who received metformin and another antihyperglycemic agent were randomized to the addition of linagliptin 5 mg once daily or to placebo after a run-in period of approximately 6 weeks of metformin ≥1500 mg daily monotherapy. Patients who failed to meet specific glycemic goals during the studies received glimepiride rescue.11

Table 1 Glycemic Parameters with Linagliptin and Metformin, Alone and in Combination, in Patients with Type 2 Diabetes: 24-Week Study

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Linagliptin 5 mg, once daily</th>
<th>Metformin 500 mg, twice daily</th>
<th>Linagliptin 2.5 mg + metformin 500 mg, twice daily</th>
<th>Metformin 1000 mg, twice daily</th>
<th>Linagliptin 2.5 mg + metformin 1000 mg, twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>A₁c Patients, N</td>
<td>65</td>
<td>135</td>
<td>141</td>
<td>137</td>
<td>138</td>
<td>140</td>
</tr>
<tr>
<td>Baseline, mean, %</td>
<td>8.7</td>
<td>8.7</td>
<td>8.7</td>
<td>8.7</td>
<td>8.5</td>
<td>8.7</td>
</tr>
<tr>
<td>Change from baseline, adjusted mean, %</td>
<td>0.1</td>
<td>−0.5</td>
<td>−0.6</td>
<td>−1.2</td>
<td>−1.1</td>
<td>−1.6</td>
</tr>
<tr>
<td>Difference from placebo, adjusted mean, %</td>
<td>—</td>
<td>−0.6</td>
<td>−0.8</td>
<td>−1.3</td>
<td>−1.2</td>
<td>−1.7</td>
</tr>
<tr>
<td>Patients achieving A₁c &lt;7%, N (%)</td>
<td>7 (10.8)</td>
<td>14 (10.4)</td>
<td>27 (19.1)</td>
<td>42 (30.7)</td>
<td>43 (31.2)</td>
<td>76 (54.3)</td>
</tr>
<tr>
<td>FPG Patients, N</td>
<td>61</td>
<td>134</td>
<td>136</td>
<td>135</td>
<td>132</td>
<td>136</td>
</tr>
<tr>
<td>Baseline, mean, mg/dL</td>
<td>203</td>
<td>195</td>
<td>191</td>
<td>199</td>
<td>191</td>
<td>196</td>
</tr>
<tr>
<td>Change from baseline, adjusted mean, mg/dL</td>
<td>10</td>
<td>−9</td>
<td>−16</td>
<td>−33</td>
<td>−32</td>
<td>−49</td>
</tr>
<tr>
<td>Difference from placebo, adjusted mean, mg/dL</td>
<td>—</td>
<td>−19</td>
<td>−26</td>
<td>−43</td>
<td>−42</td>
<td>−60</td>
</tr>
</tbody>
</table>

*Total daily dose of linagliptin is 5 mg.
FPG indicates fasting plasma glucose.
Source: Jentadueto (linagliptin/metformin HCl) tablets. Prescribing information. Ridgefield, CT: Boehringer Ingelheim; January 2012.
Active Controlled Study versus Glimepiride in Combination with Metformin Study

Linagliptin plus metformin was compared with glimepiride plus metformin in a 104-week, double-blind noninferiority study in 1552 patients with type 2 diabetes who had inadequate glycemic control despite metformin therapy.12 Patients who received metformin monotherapy entered a 2-week run-in period; those who had previously received metformin and 1 additional antihyperglycemic agent entered a 6-week run-in treatment period with metformin monotherapy 1500 mg daily and washout of the other agent. After an additional 2-week placebo run-in period, patients with inadequate glycemic control were randomized in a 1:1 ratio to the addition of linagliptin 5 mg once daily or to glimepiride 1 mg daily titrated to a maximum of 4 mg daily to optimize glycemic control.12

Add-On Combination Therapy with Metformin and a Sulfonylurea Study

In a randomized, double-blind, placebo-controlled study, 1058 patients with type 2 diabetes who received a sulfonylurea and metformin were randomized to receive linagliptin 5 mg once daily or placebo for 24 weeks (Table 2).13 The most common sulfonylureas used in the study were glimepiride, glibenclamide, and gliclazide (not available in the United States). Patients who failed to meet specific glycemic goals during the study received pioglitazone rescue. The primary glycemic end points were levels of HbA1c and fasting plasma glucose (FPG) levels.

Table 2 Glycemic Parameters with Linagliptin in Combination with Metformin and a Sulfonylurea: 24-Week Study

<table>
<thead>
<tr>
<th></th>
<th>Linagliptin 5 mg + metformin + sulfonylurea</th>
<th>Placebo + metformin + sulfonylurea</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients, N</td>
<td>778</td>
<td>262</td>
</tr>
<tr>
<td>Baseline, mean, %</td>
<td>8.2</td>
<td>8.1</td>
</tr>
<tr>
<td>Change from baseline, adjusted mean, %</td>
<td>–0.7</td>
<td>–0.1</td>
</tr>
<tr>
<td>Difference from placebo, adjusted mean, %</td>
<td>–0.6 (95% CI, –0.7, –0.5)</td>
<td>—</td>
</tr>
<tr>
<td>Patients achieving A1c &lt;7%, N (%)</td>
<td>243 (31.2)</td>
<td>24 (9.2)</td>
</tr>
<tr>
<td>FPG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients, N</td>
<td>739</td>
<td>248</td>
</tr>
<tr>
<td>Baseline, mean, mg/dL</td>
<td>159</td>
<td>163</td>
</tr>
<tr>
<td>Change from baseline, adjusted mean, mg/dL</td>
<td>–5</td>
<td>8</td>
</tr>
<tr>
<td>Difference from placebo, adjusted mean, mg/dL</td>
<td>–13 (95% CI, –18, –7)</td>
<td>—</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; FPG, fasting plasma glucose. Source: Jentadueto (linagliptin/metformin HCl) tablets. Prescribing information. Ridgefield, CT: Boehringer Ingelheim; January 2012.

Efficacy

Initial Combination Therapy

Initial therapy with linagliptin and metformin hydrochloride combination provided significant improvements in HbA1c and FPG levels compared with placebo, metformin alone, and linagliptin alone (Table 1).10

Linagliptin as Add-On to Metformin

At the end of this placebo-controlled study of linagliptin as add-on therapy to metformin, the reduction in HbA1c was –0.49% with linagliptin versus an increase of 0.15% with placebo, for a treatment difference of –0.64% (P <.001).11 A significantly higher percentage of patients in the linagliptin group achieved HbA1c <7% compared with the placebo group (26% vs 9%, respectively; P = .001). Rescue glycemic therapy was used in 7.8% of the patients who received linagliptin versus 18.9% of the placebo recipients.11

Active Controlled Study versus Glimepiride in Combination with Metformin

In this study, reductions in adjusted mean HbA1c levels were similar in the linagliptin (–0.16%) and glimepiride (–0.36%) groups, with a difference of 0.20%, which met the predefined noninferiority criterion of 0.35%.12 Fewer patients had hypoglycemia (7% vs 36%, respectively; P <.001) or severe hypoglycemia (<1% vs 2%, respectively) with linagliptin compared with glimepiride.12

Add-On Combination Therapy with Metformin and a Sulfonylurea

In combination with a sulfonylurea and metformin, linagliptin was associated with significant improvements in HbA1c and FPG levels compared with placebo (Table 2).11 In this study comprised of patients receiving linagliptin in combination with a sulfonylurea and metformin, the mean reductions from baseline were HbA1c –0.6% and FPG –12.7 mg/dL relative to placebo. Rescue therapy was used in 5.4% of the patients receiving linagliptin versus 13% of those receiving placebo.12

Safety Profile, Warnings, and Precautions

The safety of linagliptin at a 5-mg daily dose and metformin hydrochloride at a mean daily dose of approximately 1800 mg administered concomitantly has been evaluated in 2816 patients with type 2 diabetes for at
least 12 weeks. In the 3 placebo-controlled clinical studies, nasopharyngitis and nausea occurred in ≥5% of the patients receiving linagliptin and metformin together, and were more common in the linagliptin plus metformin hydrochloride cohort than in those randomized to placebo plus metformin hydrochloride (Table 3). Hypoglycemia was more common in patients treated with the combination of linagliptin plus metformin and sulfonylurea compared with those treated with the combination of placebo, sulfonylurea, and metformin. Pancreatitis was reported more often in patients randomized to linagliptin than in those receiving comparator agents (1 per 538 person-years vs 0 per 433 person-years, respectively).

The FDA approval of Jentadueto includes a Boxed Warning regarding the risk for lactic acidosis. Lactic acidosis is a rare risk of metformin accumulation. In more than 20,000 patient-years of exposure to metformin in clinical trials, there were no reports of lactic acidosis.

The risk of lactic acidosis with metformin increases with renal impairment, sepsis, dehydration, excess alcohol intake, hepatic impairment, and acute congestive heart failure. The risk can be minimized by regularly monitoring renal function. If lactic acidosis is suspected, linagliptin plus metformin hydrochloride should be discontinued and the patient should be hospitalized immediately.

### Drug Interactions

Linagliptin is a weak-to-moderate inhibitor of the cytochrome (CYP) isozyme CYP3A4, but it does not inhibit other CYP enzymes. It is a P-glycoprotein (P-gp) substrate, and it inhibits P-gp–mediated transport of digoxin at high concentrations. Linagliptin is considered unlikely to cause interactions with other P-gp substrates at therapeutic concentrations.

Inducers of CYP3A4 or P-gp (eg, rifampin) decrease exposure to linagliptin to subtherapeutic, and likely ineffective, concentrations. For patients requiring the use of such drugs, an alternative to linagliptin is strongly recommended. No dose adjustment of linagliptin is recommended based on the results of the described pharmacokinetic studies.

### Table 3

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Adverse Reactions in ≥5% of Patients Receiving Linagliptin plus Metformin and More than with Placebo: 24-Week Factorial-Design Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N = 72) N (%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (2.8)</td>
</tr>
</tbody>
</table>

Source: Jentadueto (linagliptin/metformin HCl) tablets. Prescribing information. Ridgefield, CT: Boehringer Ingelheim; January 2012.

### Conclusion

The combination of linagliptin plus metformin hydrochloride in a single tablet provides another therapeutic option to achieve glycemic control in patients with type 2 diabetes whose disease is inadequately controlled by lifestyle measures alone or by lifestyle measures combined with metformin monotherapy. According to recent guidelines, initiating therapy with dual antihyperglycemic agents may be appropriate in certain populations of patients with Hba1c levels >9%. Preliminary evidence suggests that there is a reduction in CV risk when patients are treated with DPP-4 inhibitors relative to other oral antidiabetic agents.

### References