Therapeutic Class Review
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Therapeutic Class

- **Overview/Summary:** A significant advancement in the management of type 2 diabetes has been the development of incretin-based therapies. This novel therapeutic approach is important as type 2 diabetics have been shown to have an impaired incretin response. Currently, there are two classes of incretin-based therapies available: the dipeptidyl peptidase-4 (DPP-4) inhibitors and the glucagon-like peptide-1 receptor agonists, or incretin mimetics. The DPP-4 inhibitors include alogliptin, linagliptin, saxagliptin, and sitagliptin, which are all available as single-entity agents (alogliptin [Nesina®], linagliptin [Tradjenta®], saxagliptin [Onglyza®], and sitagliptin [Januvia®]) or in fixed-dose combination products (alogliptin/metformin [Kazano®], alogliptin/pioglitazone [Oseni®], linagliptin/empagliflozin [Glyxambi®], linagliptin/metformin [Jentadueto®], saxagliptin/metformin [Kombiglyze ER®], and sitagliptin/metformin [Janumet®, Janumet XR®]). The DPP-4 inhibitors are Food and Drug Administration (FDA)-approved as adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes. Single-entity and combination agents containing alogliptin are available for use either as monotherapy or in combination with other antidiabetic agents. The fixed-dose combination products are available for use when treatment with both drug components is appropriate.

The DPP-4 inhibitors reversibly block the DPP-4 enzyme, which is responsible for the rapid degradation of endogenous incretin hormones. These hormones are produced by the gastrointestinal tract in response to meals and are involved in the regulation of insulin. The antidiabetic actions of endogenous incretin hormones include the enhancement of meal-stimulated insulin secretion, decreased glucagon secretion, improvements in β cell function, and slowing of gastric emptying. Through their effect on these hormones, the DPP-4 inhibitors primarily target post-prandial glucose and have also been shown to decrease fasting plasma glucose. In general, the DPP-4 inhibitors are associated with a favorable side effect profile and also have a weight neutral effect compared to other antidiabetic agents commonly used in the management of type 2 diabetes. Compared to sulfonylureas, the risk of hypoglycemia associated with the DPP-4 inhibitors is low due to the glucose-dependent nature of incretin hormone activity. In addition, the DPP-4 inhibitors have not been associated with the same increased risk of cardiovascular disease that has been observed with the use of thiazolidinediones (TZDs). The DPP-4 inhibitors improve the function of β cells and although TZDs and metformin treat insulin resistance, these agents do not address the progressive decline in β cell function that is observed in patients with type 2 diabetes.

The DPP-4 inhibitors are available as fixed-dose combination products with metformin. Metformin, a biguanide, improves glucose tolerance in type 2 diabetics by lowering both basal and postprandial plasma glucose. Specifically, the actions of metformin result in decreased hepatic glucose production, decreased intestinal absorption of glucose, and improvement in insulin sensitivity via increased peripheral glucose uptake and utilization. Additionally, alogliptin is available in a fixed-dose combination with pioglitazone. Pioglitazone is a TZD, an agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in adipose, skeletal muscle, and liver tissue and activation of these receptors modulates transcription of insulin response genes that control glucose and lipid metabolism, providing an overall effect of increasing insulin sensitivity in muscle and adipose tissue while inhibiting hepatic gluconeogenesis. Linagliptin is available as a fixed-dose combination with empagliflozin (Glyxambi®). Empagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor and improves glycemic control by producing glucosuria. This is accomplished by inhibiting SGLT2 and increasing urinary glucose excretion. The net effect is an increase excretion of glucose from the body and normalization of plasma glucose levels. Overall, the DPP-4 inhibitors are significantly more effective compared to placebo in reducing glycosylated hemoglobin (HbA1c), fasting plasma glucose, and post-prandial glucose, with no major effect on body weight. Combination therapy with a DPP-4 inhibitor and metformin consistently demonstrates improved benefits in glycemic control over monotherapy with either a DPP-4 inhibitor or metformin; limited within class head-to-head trials have been conducted.
Two meta-analyses revealed that DPP-4 inhibitors are not associated with an increased risk of cardiovascular events or cancer compared to placebo or other antidiabetic agents, respectively. However, a recent clinical trial suggested an increased risk of heart-failure with saxagliptin compared to placebo. In April 2016, the FDA added heart failure warnings to the labeling of medications containing saxagliptin and alogliptin.

With regards to the specific DPP-4 inhibitor agents, all single-entity agents are available for once-daily dosing. Three fixed-dose combination products contain metformin immediate-release (alogliptin/metformin [Kazano®], linagliptin/metformin [Jentadueto®] and sitagliptin/metformin [Janumet®]) which are available for twice-daily dosing. One fixed-dose combination product (alogliptin/pioglitazone [Oseni®]) contains pioglitazone and is dosed once daily. Two fixed-dose combination products contain metformin extended-release (ER) (saxagliptin/metformin ER [Kombiglyze XR®] and sitagliptin/metformin ER [Janumet XR®]), and because of the metformin ER component, these products are available for once-daily dosing. The fixed-dose combination product containing linagliptin and empagliflozin (Glyxambi®) is also available for once-daily dosing. Single-entity linagliptin is the only agent within the class that does not require renal and hepatic dosing. The fixed-dose combination of alogliptin/pioglitazone [Oseni®] carries a boxed warning regarding the risk of use in patients with congestive heart failure as the TZD component may cause or exacerbate congestive heart failure in some patients. Furthermore, because of the metformin component in certain fixed-dose combination products, caution is recommended with both renal and hepatic dysfunction. Currently, alogliptin, alogliptin/metformin, and alogliptin/pioglitazone are available generically.

Table 1. Medications Included Within the Therapeutic Class Review

<table>
<thead>
<tr>
<th>Generic (Trade Name)</th>
<th>Food and Drug Administration-Approved Indications</th>
<th>Dosage Form/Strength</th>
<th>Generic Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single-Entity Agents</strong></td>
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<tr>
<td>Alogliptin (Nesina®)</td>
<td>Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes</td>
<td>Tablet: 6.25 mg, 12.5 mg, 25 mg</td>
<td>✔</td>
</tr>
<tr>
<td>Linagliptin (Tradjenta®)</td>
<td>Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes</td>
<td>Tablet: 5 mg</td>
<td>-</td>
</tr>
<tr>
<td>Saxagliptin (Onglyza®)</td>
<td>Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes</td>
<td>Tablet: 2.5 mg, 5 mg</td>
<td>-</td>
</tr>
<tr>
<td>Sitagliptin (Januvia®)</td>
<td>Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes</td>
<td>Tablet: 25 mg, 50 mg, 100 mg</td>
<td>-</td>
</tr>
<tr>
<td><strong>Combination Products</strong></td>
<td></td>
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<tr>
<td>Alogliptin/metformin (Kazano®)</td>
<td>Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes</td>
<td>Tablet (alogliptin/metformin): 12.5/500 mg, 12.5/1,000 mg</td>
<td>✔</td>
</tr>
<tr>
<td>Alogliptin/pioglitazone (Oseni®)</td>
<td>Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes</td>
<td>Tablet (alogliptin/pioglitazone): 12.5/15 mg</td>
<td>✔</td>
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### Therapeutic Class Overview: dipeptidyl peptidase-4 (DPP-4) inhibitors

<table>
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<tr>
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<th>Dosage Form/Strength</th>
<th>Generic Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>diabetes</td>
<td>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes*</td>
<td>12.5/30 mg 12.5/45 mg 25/15 mg 25/30 mg 25/45 mg</td>
<td>-</td>
</tr>
<tr>
<td>Linagliptin/empagliflozin (Glyxambi®)</td>
<td>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes*</td>
<td>Tablet (linagliptin/empagliflozin): 5/10 mg 5/25 mg</td>
<td>-</td>
</tr>
<tr>
<td>Linagliptin/metformin (Jentadueto®)</td>
<td>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes†</td>
<td>Tablet (linagliptin/metformin): 2.5/500 mg 2.5/850 mg 2.5/1,000 mg</td>
<td>-</td>
</tr>
<tr>
<td>Saxagliptin/metformin (Kombiglyze XR®)</td>
<td>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes‡</td>
<td>Tablet (saxagliptin/metformin ER): 5/500 mg 2.5/1,000 mg 5/1,000 mg</td>
<td>-</td>
</tr>
<tr>
<td>Sitagliptin/metformin (Janumet®, Janumet XR®)</td>
<td>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes§</td>
<td>Tablet (sitagliptin/metformin): 50/500 mg 50/1,000 mg Tablet (sitagliptin/metformin ER): 50/500 mg 50/1,000 mg 100/1,000 mg</td>
<td>-</td>
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*When treatment with both linagliptin and empagliflozin is appropriate.  
†When treatment with both linagliptin and metformin is appropriate.  
‡When treatment with both saxagliptin and metformin extended-release is appropriate.  
§When treatment with both sitagliptin and metformin or metformin extended-release is appropriate.  
ER=extended-release, XR=extended-release

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**Evidence-based Medicine**

- Clinical trials have demonstrated the safety and efficacy of the dipeptidyl peptidase-4 (DPP-4) inhibitors in the management of type 2 diabetes.\(^{16-63,65-68,76,77}\) Of note, there have been minimal clinical efficacy or safety trials conducted with any of the DPP-4 inhibitor fixed-dose combination products; bioequivalence of these products with co-administration of the individual drug components has been demonstrated for all tablet strengths.\(^{6-12}\) Available trials evaluating the fixed-dose combination of sitagliptin/metformin support its efficacy and safety in the management of type 2 diabetes. Specifically, combination therapy was associated with significantly improved glycemic control compared to metformin monotherapy.\(^{57}\)

- In studies, alogliptin was associated with significant decreases in HbA\(^{1c}\) from baseline as monotherapy compared to placebo. In addition, in studies with metformin or pioglitazone combination therapy with alogliptin, significant decreases in HbA\(^{1c}\) were observed and more patients reached specific HbA\(^{1c}\) goals compared to the monotherapy comparator. As an add-on therapy in patients already being treated with metformin, pioglitazone, metformin/pioglitazone, glipizide or insulin therapy, the additions of alogliptin demonstrated significant improvements in HbA\(^{1c}\) from baseline compared to placebo.\(^{16-23}\)

- Overall, linagliptin is more effective compared to placebo in decreasing HbA\(^{1c}\) and fasting plasma glucose (FPG) as monotherapy or as add-on therapy to other antidiabetic agents in type 2 diabetics.
Therapeutic Class Overview: dipeptidyl peptidase-4 (DPP-4) inhibitors

not achieving glycemic goals. In addition, more patients achieved glycemic goals (HbA1c <7.0%) with linagliptin compared to placebo.24-27 Combination therapy with linagliptin and pioglitazone has been shown to be more efficacious in terms of reducing HbA1c compared to pioglitazone monotherapy.53

- Similar results were achieved with saxagliptin when compared to placebo. 29-36 In addition, combination therapy with saxagliptin and metformin was “superior” to monotherapy with either agent in observed reductions in HbA1c, FPG, and post-prandial glucose (PPG), and a significantly greater proportion of patients achieved glycemic goals with combination therapy.55,56

- Similar to the results of clinical trials evaluating other DPP-4 inhibitors, sitagliptin is consistently more efficacious in improving glycemic control compared to placebo, and combination therapy with sitagliptin and metformin is more efficacious than monotherapy with either agent.40-51

- In a single head-to-head trial, saxagliptin demonstrated non-inferiority to sitagliptin in reducing HbA1c. However, a significantly greater proportion of patients achieved an HbA1c ≤6.5% and achieved significant reductions in FPG with sitagliptin compared to saxagliptin.52 While the beneficial effects of the DPP-4 inhibitors in improving HbA1c, FPG, and PPG compared to placebo are well established, observed improvements in body weight and β cell function with these agents are not consistent.16-63,64

- In general, meta-analyses and systematic reviews evaluating incretin-based therapies, including the DPP-4 inhibitors, support the results observed in randomized-controlled trials evaluating these agents.37,54,62-64,65-68 Two meta-analyses revealed that DPP-4 inhibitors are not associated with an increased risk of cardiovascular events or cancer compared to placebo or other antidiabetic agents, respectively.37,61

Key Points within the Medication Class

- According to Current Clinical Guidelines for the management of type 2 diabetes:69-73,78-80
  - Metformin remains the cornerstone of most antidiabetic treatment regimens.
  - Additionally, patients with a high HbA1c will likely require combination or triple therapy in order to achieve glycemic goals.
  - At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered.
  - The DPP-4 inhibitors are recommended as a potential second-line treatment option to be added in combination with metformin in patients not achieving glycemic goals.
  - Clinical guidelines note a lower rate of hypoglycemia and an established efficacy and safety profile when used in combination with metformin as advantages associated with the DPP-4 inhibitors compared to other classes of antidiabetic agents.
  - Patients who are not appropriate for initial therapy with metformin may be initiated on another oral antidiabetic agent, such as a sulfonylurea/glinide, pioglitazone, or a DPP-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of therapy, initial therapy with an incretin mimetic may be useful. Among all current clinical guidelines, preference of one DPP-4 inhibitor over another is not stated.

- Other Key Facts:
  - All single-entity agents are available for once-daily dosing.2-5
  - Single-entity linagliptin is the only agent within the class that does not require renal and hepatic dosing.3
  - The metformin component in certain fixed-dose combination products requires caution in patients with renal and hepatic dysfunction.6-10
  - The DPP-4 inhibitors are associated with low risk of hypoglycemia and is weight neutral when used as monotherapy.5-12
  - DPP-4 inhibitors improve the function of β cells in the pancreas.1-13-15

References
Therapeutic Class Overview: dipeptidyl peptidase-4 (DPP-4) inhibitors


56. Pfützner A, Pax-Pacheco E, Allen E, Frederich R, Chen R; CV181039 Investigators. Initial combination therapy with saxagliptin and metformin provides sustained glycemic control and is well tolerated for up to 76 weeks. Diabetes Obes Metab. 2011 Jun;13(6):567-76.


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