Therapeutic Class Overview
Meglitinides

Therapeutic Class
• **Overview/Summary:** The meglitinides and the sulfonylureas are two classes of oral antidiabetic medications utilized in the management of type 2 diabetes mellitus that work by stimulating the release of insulin from pancreatic β-cells. While the meglitinide and sulfonylurea agents differ in chemical structure and act on different receptors, both medication classes act by regulating potassium channels in pancreatic β-cells, thereby increasing insulin secretion.¹ The available meglitinides, nateglinide (Starlix®) and repaglinide (Prandin®), are Food and Drug Administration (FDA)-approved as adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Nateglinide and repaglinide are both available as single-entity agents, and repaglinide is also available as a fixed-dose combination product with metformin (PrandiMet®). 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. The repaglinide/metformin combination product is FDA-approved for patients already treated with a meglitinide and metformin or for patients who have inadequate glycemic control on a meglitinide or metformin alone. Due to their mechanism of action and pharmacokinetic profiles, the meglitinides are dosed three times daily with meals.²-⁴ Currently, nateglinide, repaglinide, and the repaglinide/metformin combination are all available generically.

Table 1. Current Medications Available in the Class²-⁴

<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>Nateglinide (Starlix®*)</td>
<td>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus</td>
<td>Tablet: 60 mg 120 mg</td>
<td>✔</td>
</tr>
<tr>
<td>Repaglinide (Prandin®)</td>
<td>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus</td>
<td>Tablet: 0.5 mg 1 mg 2 mg</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Combination Products</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Repaglinide/metformin (PrandiMet®)</td>
<td>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with a meglitinide and metformin or who have inadequate glycemic control on a meglitinide alone or metformin alone</td>
<td>Tablet: 1/500 mg 2/500 mg</td>
<td>✔</td>
</tr>
</tbody>
</table>

*Generic available in at least one dosage form or strength.

Evidence-based Medicine
• Available evidence suggests that the sulfonylureas may be associated with poorer outcomes following myocardial infarction in patients with diabetes.¹ Specifically, an increased mortality from cardiovascular disease in patients taking tolbutamine with diabetes was noted in the University Group Diabetes Study.⁵ There are no long-term trials evaluating cardiovascular outcomes or mortality in patients receiving meglitinide therapy, and whether these agents are associated with adverse outcomes following a myocardial infarction is not known at this time.¹
• Overall, meglitinides are effective in decreasing glycosylated hemoglobin (HbA₁c), fasting plasma glucose, and postprandial glucose in patients with type 2 diabetes mellitus.
• Data from limited head-to-head clinical trials, suggest that repaglinide results in greater reductions in HbA₁c and fasting plasma glucose levels compared to nateglinide.⁶-²⁸
Key Points within the Medication Class

- According to current clinical guidelines:
  - Metformin remains the cornerstone of most antidiabetic treatment regimens.
  - Patients with a high HbA1c will most 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 meglitinides are recommended as a potential second line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals.
  - Patients for whom initial therapy with metformin is not appropriate may be initiated on another oral antidiabetic agent, such as a sulfonylurea/meglitinide, pioglitazone, or a dipeptidyl peptidase-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.
  - In addition, guidelines recognize the potential use of meglitinides when postprandial hyperglycemia is present.
  - Among all current clinical guidelines, preference of one meglitinide over another is not stated.

- Other Key Facts:
  - Nateglinide is the only meglitinide that is available generically.

References