Hypoglycemics, Alpha-Glucosidase Inhibitors Review

**FDA-Approved Indications**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>FDA-Approved Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>acarbose (Precose®)</td>
<td>generic</td>
<td>Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes</td>
</tr>
<tr>
<td>miglitol (Glyset®)</td>
<td>Pfizer</td>
<td>Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes</td>
</tr>
</tbody>
</table>

**Overview**

Approximately 17.9 million people in the United States have been diagnosed with diabetes, with type 2 diabetes accounting for 90 to 95 percent of all diagnosed cases.\(^3\,^4\) In type 2 diabetes, insulin function can be impaired by two pathways: impaired insulin secretion and insulin resistance (decreased insulin sensitivity). Insulin resistance is typically the first to occur, leading to increased circulating insulin levels in the blood as a result of the decreased response from muscle tissues.

The initial effects of type 2 diabetes do not have visible symptoms, which may lead to a delay in the diagnosis of this condition. According to the American Diabetic Association (ADA), nearly six million people in the United States are living with undiagnosed diabetes.\(^5\) The long-term injurious effects of consistently elevated blood glucose levels can result in microvascular complications (e.g., diabetic nephropathy, neuropathy, retinopathy) and macrovascular complications (e.g., coronary artery disease, peripheral arterial disease, stroke).

For most patients with type 2 diabetes, initial treatment will consist of lifestyle changes and oral pharmacotherapy with metformin. Modifications to lifestyle will usually include eating a healthier diet, incorporating or increasing exercise, and weight loss. Insulin sensitivity can be restored with continued practice of these changes. If lifestyle modifications and metformin are not sufficient to manage hyperglycemia, additional oral medications or insulin can be added.

In the 2009 update to the consensus algorithm, the ADA continues not to list the alpha-glucosidase inhibitors, citing their relative clinical inferiority with respect to lowering glucose levels and/or limited clinical data.\(^6\) However, despite not being included in the consensus algorithm, the guidelines do state that these agents may be a therapeutic option in select patients to assist with achievement of glycemic goals. For this reason, alpha-glucosidase inhibitors are used as add-on therapy once other treatments are deemed insufficient or are not tolerated well.

**Pharmacology**

Both acarbose (Precose) and miglitol (Glyset) are competitive, reversible inhibitors of alpha-glucosidase. These agents prevent the breakdown of sucrose (cane sugar) and complex carbohydrates in the small intestine, thereby prolonging the absorption of carbohydrates and glucose. The net effect is a reduction in postprandial glucose concentrations while fasting glucose levels are relatively unchanged. The only effects on glucose are due to the delay in
glucose absorption. Glycemic control is improved in some patients. Additionally, mouth-to-cecum transit time is decreased, resulting in less carbohydrate absorption and greater carbohydrate elimination in the stool. Miglitol is more potent than acarbose on a milligram-to-milligram basis.

**Pharmacokinetics**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bioavailability</th>
<th>Half-Life (hr)</th>
<th>Metabolites</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>acarbose</td>
<td>Less than 2 percent</td>
<td>2</td>
<td>13; one active, with less than 2 percent of parent activity</td>
<td>Almost completely renal</td>
</tr>
<tr>
<td>(Precose)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>miglitol</td>
<td>100 percent at 25 mg;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Glyset)</td>
<td>50-70 percent at 100 mg</td>
<td>2</td>
<td>None</td>
<td>Renal: &gt;95 percent at 25 mg; Renal: &lt;95 percent at higher doses</td>
</tr>
</tbody>
</table>

**Contraindications/Warnings**

The alpha-glucosidase inhibitors are contraindicated in patients with diabetic ketoacidosis, inflammatory bowel disease, ulcerative colitis, intestinal obstruction, any chronic intestinal disease disrupting digestion/absorption, any condition that may deteriorate as a result of increased gas formation in the intestine, or hypersensitivity to acarbose (Precose), miglitol (Glyset), or their ingredients.

**Drug Interactions**

Digestive enzyme preparations containing amylase or pancreatin, for example, may reduce the effect of acarbose (Precose) or miglitol (Glyset) and should not be taken concomitantly. Given alone, neither of these agents causes hypoglycemia. However, if given in combination with a sulfonylurea or insulin, the alpha-glucosidase inhibitors can increase the hypoglycemic potential of these agents by preventing an increase in blood sugar levels.
**Adverse Effects**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Abdominal pain</th>
<th>Diarrhea</th>
<th>Flatulence</th>
<th>Skin rash</th>
<th>Low serum iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>acarbose (Precose)</td>
<td>19 (9)</td>
<td>31 (12)</td>
<td>74 (29)</td>
<td>reported</td>
<td>nr</td>
</tr>
<tr>
<td>50-300 mg three times daily</td>
<td>n=1,255</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(placebo n=999)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>miglitol (Glyset)</td>
<td>11.7 (4.7)</td>
<td>28.7 (10)</td>
<td>41.5 (12)</td>
<td>4.3 (2.4)</td>
<td>9.2 (4.2)</td>
</tr>
<tr>
<td>25-100 mg three times daily</td>
<td>n=962</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(placebo n=603)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adverse effects are reported as a percentage from product package information and should not be considered comparative. Incidences reported in the placebo group are indicated in parentheses. nr = not reported.

The frequency and severity of gastrointestinal symptoms are dose-related and decrease with time.24,25,26

**Laboratory Tests**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>acarbose (Precose)</td>
<td>Monitor serum transaminase levels (AST/ALT) every three months during the first year of treatment and periodically thereafter</td>
</tr>
<tr>
<td>miglitol (Glyset)</td>
<td>None</td>
</tr>
</tbody>
</table>

HbA1c should be monitored every three months. Fasting plasma glucose should be monitored periodically.

**Special Populations**27,28

**Pediatrics**

The safety and efficacy of these agents have not been established in pediatrics.

**Pregnancy**

Both products are Pregnancy Category B.

**Renal impairment**

Both acarbose (Precose) and miglitol (Glyset) levels are elevated in patients with severe renal impairment (creatinine clearance < 25 mL/minute). Safety information is limited, and treatment with these agents is not recommended.
Liver impairment

Elevated serum transaminases, jaundice, fulminant hepatitis, and death have been reported in patients taking acarbose. Monitoring of liver function tests is recommended, and therapy is contraindicated in patients with cirrhosis.

Dosages

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose</th>
<th>Maximum Dose</th>
<th>Availability</th>
</tr>
</thead>
</table>
| acarbose (Precose)
29 mg three times daily | ≤60 kg = 50 mg three times daily >60 kg = 100 mg three times daily | 25, 50, 100 mg tablets |
| miglitol (Glyset)
25 mg three times daily | 100 mg three times daily | 25, 50, 100 mg tablets |

Doses are to be taken at the beginning of each meal.

Clinical Trials

Search Strategies

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled comparative trials for FDA-approved indications are considered the most relevant in this category. Clinical outcome trials rather than surrogate markers as trial primary outcome parameters are considered the most relevant in this class. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

acarbose (Precose)

To evaluate the effect of decreasing postprandial hyperglycemia with acarbose on the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance (IGT), an international, multicenter, double-blind, placebo-controlled, randomized trial (STOP-NIDDM) was performed. A total of 1,429 patients were enrolled in a modified intent-to-treat analysis. These patients were followed for a mean of 3.3 years. Patients with IGT were randomized to receive either placebo (n=715) or 100 mg of acarbose three times daily (n=714). Three hundred forty-one patients (24 percent) discontinued their participation prematurely, 211 in the acarbose-treated group and 130 in the placebo group. Decreasing postprandial hyperglycemia with acarbose was associated with a 49 percent relative risk reduction in the development of cardiovascular events (p=0.03) and a 2.5 percent absolute risk reduction. Among cardiovascular events, the major risk reduction was in the risk of myocardial infarction [hazard ratio (HR)=0.09; p=0.02]. Acarbose was also associated with a 34 percent relative risk
reduction in the incidence of new cases of hypertension (p=0.006) and a 5.3 percent absolute risk reduction. Even after adjusting for major risk factors, the reduction in the risk of cardiovascular events (HR=0.47; p=0.02) and hypertension (HR=0.62; p=0.004) associated with acarbose treatment was still statistically significant. This study suggests that treating IGT patients with acarbose is associated with a significant reduction in the risk of cardiovascular disease and hypertension.

The results of STOP-NIDDM were again tested by the Early Diabetes Intervention Program (EDIP).32 In 219 subjects with early diabetes (fasting plasma glucose [FPG]<140 mg/dL and two-hour plasma glucose >200 mg/dL), 100 mg acarbose three times daily or placebo were randomly assigned in a double-blind manner. Patients were followed for five years or until they reached the primary outcome (two consecutive quarterly FPG measurements of ≥140 mg/dL). Acarbose significantly reduced postprandial hyperglycemia; however, there was no difference in the cumulative rate of fasting hyperglycemia compared to placebo (29 versus 34 percent, respectively; p=0.65). There were no significant differences between groups in oral glucose tolerance test values, measures of insulin resistance, or secondary measures of beta-cell function. In a post hoc analysis of subjects with initial FPG <126 mg/dL, acarbose reduced the rate of development of FPG ≥126 mg/dL compared to placebo (27 versus 50 percent; p=0.04).

miglitol (Glyset) versus acarbose (Precose)

In a placebo-controlled, 24-week trial, 606 patients were randomized to receive placebo, 50 mg, or 100 mg of miglitol three times daily or 100 mg acarbose three times daily.33 Baseline mean HbA1c ranged from 7.56 to 7.64 percent. Actual mean changes from baseline in HbA1c were as follows: placebo, +0.21 percent; acarbose 100 mg, -0.24 percent; miglitol 50 mg, -0.27 percent; and miglitol 100 mg, -0.42 percent. Side effects are reported in Table 1. The percentages of patients discontinuing treatment due to side effects were as follows: placebo, 5.4 percent; miglitol 50 mg, 6.1 percent; miglitol 100 mg, 8.4 percent; and acarbose 100 mg, 8.3 percent. This study is “data on file” from the manufacturer of Precose and is not published.

Table 1: Percentage of patients reporting GI side effects in any treatment arm

<table>
<thead>
<tr>
<th>Drug</th>
<th>Abdominal pain</th>
<th>Diarrhea</th>
<th>Flatulence</th>
<th>Dyspepsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>placebo (n=148)</td>
<td>1.4</td>
<td>4.1</td>
<td>6.8</td>
<td>2.7</td>
</tr>
<tr>
<td>acarbose (Precose) 100 mg (n=156)</td>
<td>0.6</td>
<td>7.1</td>
<td>35.6</td>
<td>1.9</td>
</tr>
<tr>
<td>miglitol (Glyset) 50 mg (n=148)</td>
<td>3.4</td>
<td>8.1</td>
<td>16.2</td>
<td>3.4</td>
</tr>
<tr>
<td>miglitol (Glyset) 100 mg (n=154)</td>
<td>1.3</td>
<td>13</td>
<td>24</td>
<td>2.6</td>
</tr>
</tbody>
</table>
Summary

Both acarbose (Precose) and miglitol (Glyset) can be used as adjunctive therapy for the treatment of type 2 diabetes. However, their use is limited not only by their relatively lower effectiveness compared with other oral antidiabetic agents, but also due to their respective adverse effect profiles.

References