Hypoglycemics, Alpha-Glucosidase Inhibitors Review

01/07/2010

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCREditor@magellanhealth.com.

PROVIDER SYNERGIES L.L.C.
Together, we can do more.

FDA-Approved Indications

Drug	Manufacturer	FDA-Approved Indications
acarbose (Precose®)[1]	generic	Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes
miglitol (Glyset®)[2]	Pfizer	Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes

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.[7] Glycemic control is improved in some patients.[8,9,10,11] Additionally, mouth-to-cecum transit time is decreased, resulting in less carbohydrate absorption and greater carbohydrate elimination in the stool.[12] Miglitol is more potent than acarbose on a milligram-to-milligram basis.[13,14,15]

Pharmacokinetics

Drug	Bioavailability	Half-Life (hr)	Metabolites	Excretion
acarbose (Precose)[16]	Less than 2 percent	2	13; one active, with less than 2 percent of parent activity	Almost completely renal
miglitol (Glyset)[17]	100 percent at 25 mg; 50-70 percent at 100 mg	2	None	Renal: >95 percent at 25 mg; Renal: <95 percent at higher doses

Contraindications/Warnings[18,19]

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[20,21]

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

Drug	Abdominal pain	Diarrhea	Flatulence	Skin rash	Low serum iron
acarbose (Precose)[22] 50-300 mg three times daily n=1,255 (placebo n=999)	19 (9)	31 (12)	74 (29)	reported	nr
miglitol (Glyset)[23] 25-100 mg three times daily n=962 (placebo n=603)	11.7 (4.7)	28.7 (10)	41.5 (12)	4.3 (2.4)	9.2 (4.2)

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

Drug	Monitoring
acarbose (Precose)	Monitor serum transaminase levels (AST/ALT) every three months during the first year of treatment and periodically thereafter
miglitol (Glyset)	None

HbA_1c 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

Drug	Initial Dose	Maximum Dose	Availability
acarbose (Precose)[29]	25 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)[30]	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.[31] 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 HbA_1c ranged from 7.56 to 7.64 percent. Actual mean changes from baseline in HbA_1c 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

Drug	Abdominal pain	Diarrhea	Flatulence	Dyspepsia
placebo (n=148)	1.4	4.1	6.8	2.7
acarbose (Precose) 100 mg (n=156)	0.6	7.1	35.6	1.9
miglitol (Glyset) 50 mg (n=148)	3.4	8.1	16.2	3.4
miglitol (Glyset) 100 mg (n=154)	1.3	13	24	2.6

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

[1] Precose [package insert]. Wayne, NJ; Bayer; August 2008.
[2] Glyset [package insert]. New York, NY; Pfizer; September 2009.
[3] American Diabetes Association 2007 National Diabetes Fact Sheet. http://www.cdc.gov/diabetes/pubs/estimates07.htm#1. Accessed January 4, 2010.
[4] National Institute of Diabetes and Digestive and Kidney Disease (NIDDK), NIH National Diabetes Statistics, 2007. http://diabetes.niddk.nih.gov/dm/pubs/statistics/#allages. Accessed January 4, 2010..
[5] American Diabetes Association 2007 National Diabetes Fact Sheet. http://www.cdc.gov/diabetes/pubs/estimates07.htm#1. Accessed January 4, 2010.
[6] American Diabetes Association Consensus Statement. Diabetes Care. 2009; 32 (Supplement 1):193-203.
[7] Sels JP, et al. Miglitol (Bay m 1099) has no extraintestinal effects on glucose control in healthy volunteers. Br J Clin Pharmacol. 1996; 42:503-506.
[8] Taylor RH, et al. Regulation of the absorption of dietary carbohydrate in man by two new glycosidase inhibitors. Gut. 1989; 27:1471-1478.
[9] Taylor RH, et al. Effect of acarbose on the 24-hour blood glucose profile and pattern of carbohydrate absorption. Diabetes Care. 1982; 5:92-96.
[10] Weintraub M, Standish R. Acarbose: An inhibitor of intestinal alpha glucosidases. Hosp Formul. 1987; 22:624-631.
[11] Clissold SP, Edwards C. Acarbose: A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential. Drugs. 1988; 35:214-243.
[12] Ladas SD, et al. Effects of alpha-glycosidase inhibitors on mouth to caecum transit time in humans. Gut. 1992; 33:1246-1248.
[13] Kennedy FP, et al. The effect of two new alpha-glucosidase inhibitors on metabolic responses to a mixed meal in normal volunteers. Clin Experimental Pharmacol Physiology. 1987; 14:633-640.
[14] Madar Z, Hazan A. Effect of miglitol and acarbose on starch digestion, daily plasma glucose profiles and cataract formation. J Basic Clin Physiol Pharmacol. 1993; 4:69-81.
[15] Joubert PH, et al. The effect of miglitol and acarbose after an oral glucose load: A novel hypoglycaemic mechanism? Br J Clin Pharmacol. 1990; 30:391-396.
[16] Precose [package insert]. Wayne, NJ; Bayer; August 2008.
[17] Glyset [package insert]. New York, NY; Pfizer; September 2009.
[18] Precose [package insert]. Wayne, NJ; Bayer; August 2008.
[19] Glyset [package insert]. New York, NY; Pfizer; September 2009.
[20] Precose [package insert]. Wayne, NJ; Bayer; August 2008.
[21] Glyset [package insert]. New York, NY; Pfizer; September 2009.
[22] Precose [package insert]. Wayne, NJ; Bayer; August 2008.
[23] Glyset [package insert]. New York, NY; Pfizer; September 2009.
[24] Precose [package insert]. Wayne, NJ; Bayer; August 2008.
[25] Glyset [package insert]. New York, NY; Pfizer; September 2009.
[26] Escobar-Jimenez F, et al. Efficacy and tolerability of miglitol in the treatment of patients with non-insulin-dependent diabetes mellitus. Curr Ther Res. 1995; 56:258-268.
[27] Precose [package insert]. Wayne, NJ; Bayer; August 2008.
[28] Glyset [package insert]. New York, NY; Pfizer; September 2009.
[29] Precose [package insert]. Wayne, NJ; Bayer; August 2008.
[30] Glyset [package insert]. New York, NY; Pfizer; September 2009.
[31] Chiasson JL, Josse RG, Gomis R, et al. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA. 2003; 290(4):486-494.
[32] Kirkman MS, Shankar RR, Shankar S, et al. Treating postprandial hyperglycemia does not appear to delay progression of early type 2 diabetes: the Early Diabetes Intervention Program. Diabetes Care. 2006; 29(9):2095-2101.
[33] Data on file, Bayer Report No. R6245 (Study 0288), NDA 20-682. Bridgewater, NJ: Pharmacia and Upjohn Company.