ACARBOSE (Systemic)

Introduction

VA CLASSIFICATION (Primary)¾HS504

Commonly used brand name(s):Precose.

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

Category

Antidiabetic agent.

Indications

Accepted

Diabetes, type 2 (treatment)¾Acarbose is indicated as an adjunctive therapy to diet in the treatment of patients with type 2 diabetes (previously referred to as non-insulin-dependent diabetes mellitus [NIDDM]) whose blood glucose cannot be controlled by diet alone. It may be used as monotherapy or in combination with a sulfonylurea. 1

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Source¾Acarbose is an oligosaccharide obtained from fermentation processes of the microorganism Actinoplanes utahensis. 1

Molecular weight¾645.6 1

pKa¾5.1 1

Mechanism of action/Effect:

Acarbose lowers postprandial blood glucose concentrations in patients with diabetes by competitive, reversible inhibition of pancreatic alpha-amylase and membrane-bound intestinal alpha-glucoside hydrolases. These enzymes inhibit hydrolysis of complex starches to oligosaccharides in the lumen of the small intestine and hydrolysis of oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides in the brush border of the small intestine. Acarbose does not enhance insulin secretion and, when used as monotherapy, should not cause hypoglycemia. 1

Other actions/effects:

Although the antihyperglycemic effect of acarbose is additive to that of sulfonylureas (which act via a different mechanism), acarbose decreases the insulinotropic and weight-increasing effects of sulfonylureas when used concurrently 1.

Acarbose does not inhibit lactase and would not be expected to cause lactose intolerance 1.

Absorption:

Studies with radiolabeled acarbose indicate that less than 2% of an oral dose is absorbed in active form. Because the medication acts within the gastrointestinal tract, low systemic bioavailability is therapeutically desirable. However, approximately 35% of a dose is absorbed on a delayed basis, probably as metabolites formed in the gastrointestinal tract. 1

Biotransformation:

Gastrointestinal, primarily by intestinal bacteria and, to a lesser extent, by digestive enzymes. At least 13 metabolites have been identified. One of these, formed by cleavage of a glucose molecule from acarbose, has alpha-glucosidase inhibitory activity. Other major metabolites are primarily sulfate, methyl, and glucuronide conjugates. 1

Half-life:

Approximately 2 hours 1.

Time to peak concentration:

In plasma¾ Acarbose: 1 hour 1.

Metabolites: 14 2 to 24 hours 1.

Elimination:

Fecal, as unabsorbed acarbose, approximately 51% of an oral dose within 96 hours 1.

Renal, approximately 34% of an oral dose as absorbed metabolites. Less than 2% of an oral dose is excreted in the urine as acarbose and its active metabolite 1.

Precautions to Consider

Carcinogenicity/Tumorigenicity

Up to 500 mg per kg of body weight (mg/kg) of acarbose administered orally to Sprague-Dawley rats for 104 weeks resulted in a significant increase in the incidence of renal adenomas and adenocarcinomas and benign Leydig cell tumors. The study was repeated with similar results. However, an increase in renal tumors did not occur in Sprague-Dawley rats when carbohydrate malnutrition was prevented by glucose supplementation or by administration of acarbose by daily postprandial gavage. Also, no evidence of tumorigenicity or carcinogenicity was found in two studies

in Wistar rats receiving acarbose by postprandial gavage or two studies in hamsters given oral acarbose with or without glucose supplementation. 1

Mutagenicity

No evidence of mutagenicity was noted in six in vitro and in three in vivo assays 1.

Pregnancy/Reproduction

Fertility¾Oral administration of acarbose to rats produced no impairment of fertility or overall reproductive capacity. 1

Pregnancy¾Adequate and well-controlled studies have not been done in humans, and safety has not been established. Insulin is usually recommended for pregnant patients with diabetes. 1

Animal studies failed to show an adverse effect on the fetus in rats given up to 480 mg/kg (approximately 9 times the human exposure, based on blood concentrations) or in rabbits given up to 32 times the human dose (based on body surface area). In rabbit studies, high doses of acarbose caused a reduction in maternal weight gain, which may have been responsible for a slight increase in embryonic losses. However, no embryotoxicity occurred in rabbits given 160 mg/kg (corresponding to 10 times the human dose, based on body surface area). 1

FDA Pregnancy Category B. 1

Breast-feeding

It is not known whether acarbose is distributed into human breast milk. In animal studies, administration of radiolabeled acarbose resulted in detection of a small quantity of radioactivity in the milk of lactating rats. 1 Acarbose is not recommended for use by nursing women. 2

Pediatrics

Safety and efficacy in pediatric patients have not been established 1.

Geriatrics

In pharmacokinetic studies, maximum plasma concentrations of acarbose and the area under the acarbose concentration-time curve (AUC) were approximately 1.5 times higher in geriatric individuals than in younger adults, but the differences were not statistically significant 1.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

>> Adsorbents, intestinal, such as activated charcoal or

>> Digestive enzyme preparations containing carbohydrate-splitting enzymes, such as amylase or pancreatin

(these medications may decrease the efficacy of acarbose; concurrent use is not recommended 1)

Antidiabetic agents, other

(antihyperglycemic effects of acarbose are additive to those of other antidiabetic agents; although this effect is used for therapeutic benefit, the risk of hypoglycemia may be increased with concurrent use; a reduction in dosage of the other antidiabetic agent may be necessary 1)

Hyperglycemia-inducing medications, such as:
Calcium channel blocking agents
Corticosteroids
Diuretics, especially thiazide diuretics
Estrogens
Estrogen and progestin-containing oral contraceptives
Isoniazid
Niacin
Phenothiazines
Phenytoin
Sympathomimetic agents
Thyroid hormones

(these agents may cause loss of glycemic control; patients should be monitored for evidence of hyperglycemia and the dosage of the antidiabetic agent adjusted if necessary; also, patients receiving combined therapy with acarbose and another antidiabetic agent should be monitored for evidence of hypoglycemia after treatment with one of these agents is discontinued 1)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With physiology/laboratory test values

Bilirubin, serum

(elevations have been reported rarely 1)

Transaminases, serum

(transaminase elevations occurred in 15% of acarbose-treated patients in clinical trials; in patients receiving a total of 150 to 300 mg of acarbose a day, elevations did not occur more often than in placebo controls, but elevations to more than three times the upper limit of normal occurred two to three times more often in patients receiving more than 300 mg per day than in placebo controls. The elevations were more common in female patients, reversible, and not associated with other

evidence of liver injury. In postmarketing surveillance of more than 500,000 patients, 19 cases of transaminase elevations to 500 IU per L or higher have been reported, 12 of which were associated with jaundice. Of these 19 patients, 15 had been receiving total doses of 300 mg or more of acarbose per day, and 13 of the 16 patients for whom weights were reported weighed less than 60 kg. Hepatic abnormalities improved or resolved after treatment was discontinued in the 18 patients for whom follow-up information is available 1)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problems exist

>> Diabetic ketoacidosis 1

>> Hepatic cirrhosis 1

(acarbose may cause transaminase elevations and, rarely, jaundice 1)

Intestinal disorders, including:
>> Chronic conditions leading to marked disorders of absorption or digestion 1

>> Conditions that would be affected adversely by increased intestinal gas formation 1

>> Inflammatory or ulcerative intestinal disease 1

>> Obstructive intestinal disease or predisposition to 1

>> Renal function impairment, severe (serum creatinine higher than 2 mg/dL)

(although long-term studies in patients with severe renal function impairment have not been done, use of acarbose is not recommended; pharmacokinetic studies have shown that plasma concentrations of acarbose increase in proportion to the degree of renal function impairment, with maximum concentrations being approximately five times higher and the area under the acarbose concentration-time curve [AUC] being approximately six times higher in patients with creatinine clearances of less than 25 mL per minute per 1.73 square meters of body surface area than in patients with normal renal function 1)

Risk-benefit should be considered when the following medical problems exist

Fever or

Infection or

Surgery or

Trauma

(these conditions may cause loss of glycemic control; temporary insulin therapy may be necessary 1)

Sensitivity to acarbose 1

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
>> Glucose concentrations, blood and/or urine

(monitoring essential as a guide to efficacy of treatment 1)

>> Glycosylated hemoglobin determinations

(recommended at 3-month intervals for monitoring long-term glycemic control 1)

>> Transaminase values

(monitoring recommended at 3-month intervals during the first year of treatment and periodically thereafter; a reduction of acarbose dosage or discontinuation of therapy may be necessary, especially if elevations persist 1)

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence rare

Jaundice 1 (yellow eyes or skin)
Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Abdominal pain 1¾incidence 21% 1; diarrhea 1¾incidence 33% 1; flatulence 1 (bloated feeling or passing of gas)¾incidence 77% 1

Note: These effects are related to the presence of undigested carbohydrates in the lower gastrointestinal tract, a result of acarbose's mechanism of action. In clinical trials, abdominal pain and diarrhea tended to return to pretreatment levels, and the frequency and severity of flatulence tended to abate, over time. Rarely, gastrointestinal effects may be severe enough to be confused with paralytic ileus. 1

Overdose

For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Clinical effects of overdose

The most likely effects are increases in abdominal discomfort, diarrhea, and flatulence, which should subside without treatment. Hypoglycemia should not occur with an overdose of acarbose alone, but can occur if the patient is receiving combined therapy with other antidiabetic agents. 1

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Acarbose (Systemic)¾Introductory Version .
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Sensitivity to acarbose
Pregnancy¾Insulin is usually recommended
Breast-feeding¾Use of acarbose is not recommended
Other medications, especially digestive enzyme preparations, or intestinal adsorbents
Other medical problems, especially diabetic ketoacidosis, hepatic cirrhosis, intestinal disorders, or renal function impairment
Proper use of this medication

>> Importance of adherence to recommended regimens for diet, exercise, and glucose monitoring

>> Taking medication at the beginning of each main meal

>> Proper dosing
Missed dose (if meal completed without having taken medication): Skipping missed dose; taking next dose with next meal; not doubling doses
>> Proper storage
Precautions while using this medication

>> Regular visits to physician to check progress

>> Carefully following special instructions of health care team

Discussing use of alcohol and tobacco

Not taking other medications unless discussed with physician

Getting counseling for family members to help them assist the diabetic patient; also, special counseling for pregnancy planning and contraception

Making travel plans to include preparedness for diabetic emergencies and keeping meal times near the usual times with changing time zones

>> Preparing for and understanding what to do in case of emergency; carrying medical history and current medication list and wearing medical identification

>> Recognizing what brings on symptoms of hypoglycemia, such as using other antidiabetic medication; delaying or missing a meal; exercising more than usual; drinking significant amounts of alcohol; illness, including vomiting or diarrhea

>> Recognizing symptoms of hypoglycemia: anxiety; behavior change similar to drunkenness; blurred vision; cold sweats; confusion; cool, pale skin; difficulty in concentrating; drowsiness; excessive hunger; fast heartbeat; headache; nausea; nervousness; nightmares; restless sleep; shakiness; slurred speech; and unusual tiredness or weakness

>> Knowing what to do if symptoms of hypoglycemia occur, such as ingesting a source of dextrose (not sucrose) or, if severe, injecting glucagon

>> Recognizing what brings on symptoms of hyperglycemia, such as not taking enough or skipping a dose of antidiabetic medication, overeating or not following meal plan, fever or infection, exercising less than usual

>> Recognizing symptoms of hyperglycemia and ketoacidosis: blurred vision; drowsiness; dry mouth; flushed, dry skin; fruit-like breath odor; increased urination (frequency and volume); ketones in urine; loss of appetite; stomachache, nausea, or vomiting; tiredness; troubled breathing (rapid and deep); unconsciousness; unusual thirst

>> Knowing what to do if symptoms of hyperglycemia occur, such as checking blood glucose and contacting a member of the health care team

Side/adverse effects

Signs of potential side effects, especially jaundice

General Dosing Information

Dosage must be individualized on the basis of 1-hour postprandial blood glucose determinations and patient tolerance. The goal of treatment is to reduce postprandial plasma glucose concentrations and glycosylated hemoglobin concentrations to normal or near normal using the lowest effective dose of acarbose, alone or in conjunction with a sulfonylurea. 1

Starting treatment with a low dose that is increased gradually to the maximally effective dose is recommended to reduce gastrointestinal side effects as well as to facilitate identification of the lowest effective dose for the individual patient 1.

Acarbose is taken three times a day, at the beginning (with the first bite) of each main meal 1.

For treatment of hypoglycemia

Hypoglycemia should not occur as a result of acarbose monotherapy, but may occur during combined therapy with a sulfonylurea or insulin. Because acarbose inhibits hydrolysis of sucrose to glucose and fructose, sucrose is not recommended for treatment of mild to moderate hypoglycemia in acarbose-treated patients. A simple sugar, such as dextrose (glucose), should be ingested instead. Intravenous infusion of dextrose or administration of glucagon may be required for severe hypoglycemia. 1

Oral Dosage Forms

ACARBOSE TABLETS

Usual adult dose

Antidiabetic agent¾Oral, 25 mg three times a day, at the start of each main meal. Dosage may be adjusted, at four- to eight-week intervals, first to 50 mg three times a day, then, if necessary and appropriate, to 100 mg three times a day. 1

Note: If an increase in dosage to 100 mg three times a day fails to produce a further reduction in postprandial glucose concentration, consideration should be given to lowering the dose. 1

Usual adult prescribing limits

Antidiabetic agent¾Patients weighing 60 kg or less: 50 mg three times a day. 1

Patients weighing more than 60 kg: 100 mg three times a day. 1

Usual pediatric dose

Safety and efficacy have not been established. 1

Usual geriatric dose

Antidiabetic agent¾See Usual adult dose 1.

Usual geriatric prescribing limits

Antidiabetic agent¾See Usual adult prescribing limits 1.

Strength(s) usually available

U.S.¾50 mg (Rx)[Precose (scored) (starch) (microcrystalline cellulose) (magnesium stearate) (colloidal silicon dioxide) 1]

100 mg (Rx)[Precose (starch) (microcrystalline cellulose) (magnesium stearate) (colloidal silicon dioxide) 1]

Packaging and storage:

Store below 25 °C (77 °F), protected from moisture, unless otherwise directed by manufacturer 1.