PRODUCT MONOGRAPH

PrGLUCOBAY™

acarbose

50 and 100 mg tablets

Oral Antidiabetic Agent

Alpha-glucosidase Inhibitor

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PrGLUCOBAY™

acarbose

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1 – Product Information Summary

Route of Administration	Dosage Form, Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet 50 mg, 100 mg	*See **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

- GLUCOBAY (acarbose), as monotherapy, is indicated as an adjunct to prescribed diet for the management of blood glucose levels in patients with type 2 diabetes mellitus who are inadequately controlled by diet alone.
- GLUCOBAY may also be used in combination with either a sulfonylurea, metformin or insulin to improve glycemic control in patients with type 2 diabetes mellitus, who are inadequately controlled on diet, exercise and either a sulfonylurea, metformin or insulin alone. The effect of GLUCOBAY in enhancing glycemic control is additive to that of sulfonylureas, metformin or insulin when used in combination, because of its different mechanism of action.

In initiating treatment for type 2 diabetes mellitus, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling blood glucose and symptoms of hyperglycemia. The importance of regular physical activity when appropriate should also be stressed. If this treatment program fails to result in adequate glycemic control, the use of GLUCOBAY should be considered. The use of GLUCOBAY must be viewed by both the physician and patient as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint. GLUCOBAY should be considered as complementary to dietary therapy and physical exercise before resorting to other forms of treatment, such as oral hypoglycemics.

Pediatrics (<18 years of age)

Safety and effectiveness of GLUCOBAY in patients <18 years of age have not been established.

Geriatrics

Elderly patients receiving GLUCOBAY may require more intensive supervision and follow-up.

CONTRAINDICATIONS

- Patients who are hypersensitive to acarbose or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.
- GLUCOBAY is contraindicated in patients with diabetic ketoacidosis.
- It is also contraindicated in patients with inflammatory bowel disease, colonic ulceration, partial intestinal obstruction or in patients predisposed to intestinal obstruction.
- In addition, GLUCOBAY should not be used in patients who have chronic intestinal diseases associated with marked disorders of digestion or absorption and in patients who suffer from states which may deteriorate as a result of increased gas formation in the intestine, eg, larger hernias.

WARNINGS AND PRECAUTIONS

General

GLUCOBAY delays glucose absorption and lowers hyperglycemia following meals. Regular intake of GLUCOBAY should not be interrupted without the physician's knowledge, since such interruption can cause a rise in blood glucose.

Carcinogenesis and Mutagenesis

There is no evidence from preclinical data that GLUCOBAY is carcinogenic or mutagenic (see PART II: SCIENTIFIC INFORMATION, TOXICOLOGY for preclinical studies).

Endocrine and Metabolism

Hypoglycemia

Because of its mechanism of action, GLUCOBAY when administered alone will not cause hypoglycemia in the fasted or postprandial state. Sulfonylurea agents or insulin may cause hypoglycemia. Because GLUCOBAY given with a sulfonylurea, metformin or insulin may cause a further lowering of blood glucose, the potential for hypoglycemia may be increased. A fall of the blood glucose into the hypoglycemic range may necessitate a suitable decrease in the sulphonylurea, metformin or insulin dose. In individual cases, hypoglycemic shock may occur.

Oral glucose (dextrose), whose absorption is not inhibited by GLUCOBAY, should be used instead of sucrose (cane sugar) in the treatment of mild to moderate hypoglycemia. Sucrose, whose hydrolysis to glucose and fructose is inhibited by GLUCOBAY, is unsuitable for the rapid

correction of hypoglycemia. Severe hypoglycemia may require the use of either intravenous glucose infusion or glucagon injection.

Loss of Control of Blood Glucose

When diabetic patients are exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of control of blood glucose may occur. At such times, temporary insulin therapy may be necessary.

Gastrointestinal

Increased use of sucrose (cane sugar) and food that contains sucrose can lead to gastrointestinal symptoms (eg, flatulence and bloating) and also loose stools and occasionally diarrhea as a result of increased carbohydrate fermentation in the colon during GLUCOBAY treatment.

If the prescribed diet is not observed, the intestinal side effects may be intensified. If strongly distressing symptoms develop in spite of adherence to the diabetic diet prescribed, the doctor must be consulted and the dose temporarily or permanently reduced.

Hepatic

In postmarketing experience with GLUCOBAY, reports of hepatic adverse events have been received, including reports of liver failure, liver transplant, and fulminant hepatitis, with and without fatal outcome. The mechanism is unknown, but GLUCOBAY may contribute to a multifactorial pathophysiology of liver injury, particularly in combination with impaired metabolic control and/or concomitant antidiabetic medications (see **ADVERSE REACTIONS - Postmarket Adverse Drug Reactions**).

GLUCOBAY may give rise to elevations of serum transaminases and, in rare instances, hyperbilirubinemia. If elevations are observed, a reduction in dosage or withdrawal of therapy may be indicated, particularly if the elevations persist. Liver enzyme monitoring should be considered during the first 6 to 12 months of treatment.

In patients with a known history of liver impairment or liver disease, liver enzymes should be measured prior to the start of GLUCOBAY therapy and monitored on a regular basis during the first year. If a clinical deterioration or increases in levels of hepatic enzymes are detected, discontinuation of treatment with GLUCOBAY should be considered.

Renal

Plasma concentrations of GLUCOBAY in renally impaired volunteers were proportionally increased relative to the degree of renal dysfunction. Long-term clinical trials in diabetic patients with severe renal dysfunction (creatinine clearance <25 mL/min) have not been conducted. Treatment of patients with severe renal dysfunction (creatinine clearance <25 mL/min) with GLUCOBAY is not recommended.

Special Populations

Pregnant Women

There are no adequate and well-controlled studies of GLUCOBAY in pregnant women and its use in these patients is not recommended.

Nursing Women

A small amount of radioactivity has been found in the milk of lactating rats after administration of radiolabelled acarbose. It is not kno

wn whether this drug is excreted in human milk. Because many drugs are excreted in human milk, GLUCOBAY should not be administered to a nursing woman.

Pediatrics (<18 years of age)

Safety and effectiveness of GLUCOBAY in patients <18 years of age have not been established.

Geriatrics

Elderly patients receiving GLUCOBAY may require more intensive supervision and follow-up.

Monitoring and Laboratory Tests

Liver enzyme monitoring should be considered during the first 6 to 12 months of treatment. In patients with a known history of liver impairment or liver disease, liver enzymes should be measured prior to the start of GLUCOBAY therapy and monitored on a regular basis during the first year (see **WARNINGS AND PRECAUTIONS - Hepatic**).

Digoxin

In individual cases, GLUCOBAY may affect digoxin bioavailability, which may require dose adjustment of digoxin.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

GLUCOBAY was administered to over 17,300 patients in clinical trials worldwide, including over 8500 in placebo-controlled trials. The most common adverse events occurring with use in placebo-controlled trials include flatulence, diarrhea, and gastrointestinal and abdominal pains.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information

from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In placebo controlled pivotal studies of ≥6 months duration where GLUCOBAY was used as monotherapy or in combination with a sulfonylurea, adverse experiences were reported in 53% of patients receiving placebo and in 77% of patients treated with GLUCOBAY. The majority of adverse experiences were gastrointestinal symptoms which result from the pharmacodynamic action of the drug. The majority of symptoms were of mild or moderate intensity and were dose-dependent. The symptoms occurred early (within 1-2 months of treatment) and improved tolerability with longer duration of treatment was observed. Therapy was discontinued prematurely due to adverse events in 14% of GLUCOBAY-treated patients and 5% of placebo-treated patients.

Adverse drug reactions (ADRs) based on placebo-controlled studies with GLUCOBAY sorted by CIOMS III categories of frequency (placebo-controlled studies in clinical trial database: GLUCOBAY N=8,595; placebo N=7,278) are listed in Table 2 below.

Table 2 – Incidence of Adverse Drug Reactions in Placebo-Controlled Studies (%)

Clinical Description	**Very Common** **>10%**	**Common** **≥1%**
Gastrointestinal Disorders		
Gastrointestinal symptoms	Flatulence	Diarrhea Gastrointestinal and abdominal pains

The only significant difference in the incidence of adverse events between GLUCOBAY and placebo were gastrointestinal symptoms (eg, flatulence, diarrhea, gastrointestinal and abdominal pain) which can be minimized by starting on a low dose and titrating slowly (see **DOSAGE AND ADMINISTRATION - Recommended Dose and Dosage Adjustment**). Adverse events seen when GLUCOBAY is used concomitantly with other antidiabetic agents are generally similar to those seen during GLUCOBAY monotherapy. If GLUCOBAY tablets are prescribed in addition to sulphonylureas, metformin, or insulin, a fall of the blood glucose values into the hypoglycemic range may necessitate a decrease in the sulphonylurea, metformin or insulin dosage. In individual cases, hypoglycemic shock may occur.

Less Common Clinical Trial Adverse Drug Reactions

The following additional adverse events occurred in ≥0.1% to <1% of patients receiving GLUCOBAY in all clinical trials:

Gastrointestinal: nausea, vomiting, dyspepsia.

Hepatic: increase in liver enzymes.

The following additional adverse events occurred in ≥0.01% to <0.1% of patients receiving GLUCOBAY in all clinical trials:

Vascular: oedema.

Hepatic: jaundice.

Abnormal Hematologic and Clinical Chemistry Findings

In clinical trials, in patients receiving the recommended daily dose of 150 to 300 mg acarbose per day, rarely clinically relevant abnormal liver function tests (three times above upper limit of normal range) were observed. Abnormal values may be transient under ongoing acarbose therapy. The incidence of serum transaminase elevations with GLUCOBAY was the same as with placebo.

Postmarket Adverse Drug Reactions

Very rarely (<0.01%), cases of hepatitis, thrombocytopenia and/or jaundice and associated liver damage have been reported. In addition, cases of serum transaminase levels > 10 x ULN have been reported, some of which were associated with jaundice. In most cases where follow-up was reported, hepatic dysfunction improved or resolved upon discontinuation of GLUCOBAY. Reports of liver failure and liver transplant, with and without fatal outcome, have been received. Events reported as liver disorder, hepatic function abnormal, and liver injury have been received, especially from Japan. Individual cases of fulminant hepatitis with fatal outcome have also been reported in Japan. Other, as yet undefined, patient populations may be similarly susceptible. (See **WARNINGS AND PRECAUTIONS - Hepatic**).

Very rarely (<0.01%), cases of subileus/ileus, pneumatosis cystoidis intestinalis, and hypersensitive skin reactions, such as rash, erythema, exanthema and urticaria, have been reported.

Rarely (≥0.01% and <0.1%), edema has been observed.

DRUG INTERACTIONS

Overview

Certain drugs tend to produce hyperglycemia and may lead to loss of blood glucose control. These drugs include diuretics (thiazides, furosemide), corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathominetics and isoniazid. When such drugs are administered to a patient receiving GLUCOBAY, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from patients receiving GLUCOBAY in combination with sulfonylureas or insulin, patients should be observed closely for evidence of hypoglycemia.

Drug-Drug Interactions

Intestinal Absorbents

Intestinal absorbents (eg, charcoal) and digestive enzyme preparations containing carbohydrate-splitting enzymes (amylase, pancreatin) may reduce the effect of GLUCOBAY and should not be taken concomitantly. No interaction was observed with dimethicone/simethicone.

Antacids

The concomitant administration of GLUCOBAY and an antacid does not alter the effect of GLUCOBAY. The administration of antacid preparations is unlikely to ameliorate the gastrointestinal symptoms of GLUCOBAY and therefore should not be recommended to patients for this purpose.

Cholestyramine

The concomitant administration of cholestyramine may enhance the effects of GLUCOBAY, particularly with respect to reducing postprandial insulin levels. In healthy volunteers, a rebound phenomenon with respect to the postprandial insulin response was observed when both GLUCOBAY and cholestyramine therapy were withdrawn simultaneously.

Digoxin

In individual cases, GLUCOBAY may affect digoxin bioavailability, which may require dose adjustment of digoxin.

Metformin

The amount of metformin absorbed while taking GLUCOBAY was bioequivalent to the amount absorbed when taking placebo, as indicated by the plasma AUC values. However, the peak plasma level of metformin was reduced by approximately 20% when taking GLUCOBAY due to a slight delay in the absorption of metformin. There is little, if any, clinically significant interaction between GLUCOBAY and metformin. Therefore, no dose modification of either agent is necessary.

Other Drugs

Studies in healthy volunteers have shown that GLUCOBAY has no effect on either the pharmacokinetics or pharmacodynamics of nifedipine, propranolol, or ranitidine.

Drug-Food Interactions

Not applicable

Drug-Herb Interactions

Drug-Herb interactions have not been established.

Drug-Laboratory Interactions

Drug-laboratory interactions have not been established.

Drug-Lifestyle Interactions

Drug-Lifestyle interactions have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

During treatment initiation and dose titration (see DOSAGE AND ADMINISTRATION: Recommended Dose and Dosage Adjustment), two-hour postprandial plasma glucose should be used to determine the therapeutic response to GLUCOBAY and identify the minimum effective dose for the patient. Thereafter, glycosylated hemoglobin should be measured at intervals of approximately three months. The therapeutic goal should be to decrease both postprandial plasma glucose and glycosylated hemoglobin levels to optimal or near optimal by using the lowest effective dose of GLUCOBAY, either as monotherapy or in combination with sulfonylureas, metformin, or insulin. (1)

Patients Receiving Sulfonylureas or Insulin

Sulfonylurea agents or insulin may cause hypoglycemia. Therefore, GLUCOBAY given in combination with a sulfonylurea or insulin may also cause hypoglycemia. If hypoglycemia occurs, appropriate adjustment in the sulfonylurea or insulin dosage should be made.

Recommended Dose and Dosage Adjustment

Initial Dosage

Dosage of GLUCOBAY must be individualized on the basis of both effectiveness and tolerance while not exceeding 100 mg t.i.d. GLUCOBAY should be started at a low dose, with gradual dose escalation as described below, both to reduce gastrointestinal side effects and to permit identification of the minimum dose required for adequate glycemic control of the patient.

The usual starting dosage of GLUCOBAY is 50 mg given orally once daily. After 1-2 weeks, the dosage should be increased to 50 mg b.i.d. with a subsequent increase to 50 mg t.i.d. after a further 1-2 weeks. Each dose should be taken with the first bite of a main meal. GLUCOBAY must always be taken together with food.

Once a maintenance dose of 50 mg t.i.d. has been reached, some patients may benefit from further increasing the dosage to 100 mg t.i.d. The maintenance dose ranges from 50 mg t.i.d. to 100 mg t.i.d. The dosage of GLUCOBAY should be adjusted at 4-8 week intervals based on two-hour postprandial glucose levels and on tolerance. Consideration should be given to lowering the dose if no further reduction in postprandial glucose or glycosylated hemoglobin levels is observed after titration to 100 mg t.i.d. Once an effective and tolerated dosage is established, it should be maintained.

Maximum Dosage

Dosages above 100 mg t.i.d. are not recommended.

Missed Dose

GLUCOBAY has to be taken at the beginning of a meal. If a dose has been missed, no effect on blood glucose and serum insulin can be expected. Should a dose be missed, the patient should not take a tablet until their next meal.

OVERDOSAGE

For management of a suspected overdose please contact your regional Poison Control Centre.

Unlike sulfonylureas or insulin, an overdose of GLUCOBAY will not result in hypoglycemia. When GLUCOBAY is taken with drinks and/or meals containing carbohydrates (polysaccharides, oligosaccarides, or disaccharides), overdosage can lead to abdominal distention, flatulence, and diarrhea. In the event of GLUCOBAY being taken in an overdose independent of food, excessive intestinal symptoms need not be anticipated.

In cases of overdosage, the patient should not be given drinks or meals containing carbohydrates (polysaccharides, oligosaccharides, and disaccharides) for the next 4 to 6 hours.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Acarbose has been shown in animal studies to be a competitive inhibitor of intestinal brush-border α-glucosidase enzymes. The inhibitory potency follows a rank order of glucoamylase > sucrase > maltase > isomaltase. Acarbose has little or no effect on lactase and trehalase. Studies in healthy volunteers demonstrated that oral doses of 75 to 300 mg acarbose taken together with a meal reduced elevated concentrations of blood glucose and serum insulin in a dose-dependent manner. A clear dose-proportionality of single oral doses of 50, 100, and 200 mg acarbose was shown in respect to an increase in blood glucose and serum insulin after simultaneous ingestion of 75 g sucrose. The inhibition of the postprandial insulin response was identical following oral administration of 1 x 100 mg and 2 x 50 mg acarbose, thus demonstrating pharmacological bioequivalence. The reduction in postprandial insulin concentrations was also found to be dose dependent in obese subjects, in whom insulin resistance is often present.

After oral administration of 200 mg acarbose, the area under the blood glucose concentration time curve was reduced by 89% after sucrose loading, and by 80% after starch loading and by 19% after maltose loading. There was no effect of acarbose observed after oral administration of lactose and glucose or after intravenous administration of glucose.

Pharmacodynamics

Acarbose is a complex oligosaccharide that inhibits α-glucosidase activity in the brush border membrane of the small intestine. This delays the digestion of ingested carbohydrates, thereby resulting in a smoothing and lowering of blood glucose concentration following meals (postprandial). As a consequence of decreases in plasma glucose postprandial increases, acarbose

reduces levels of glycosylated hemoglobin in patients with type 2 diabetes mellitus. Systemic nonenzymatic protein glycosylation, as reflected by levels of glycosylated hemoglobin, is a function of average blood glucose concentration over time.

Acarbose does not enhance insulin secretion. The antihyperglycemic action of acarbose results from a competitive, reversible inhibition of pancreatic α-amylase and membrane bound intestinal α-glucoside hydrolase enzymes. Pancreatic α-amylase hydrolyzes complex starches to oligosaccharides in the lumen of the small intestine, while the membrane-bound intestinal α-glucosidases hydrolyze oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides in the brush border of the small intestine. In diabetic patients, this enzyme inhibition results in a delayed glucose absorption and a smoothing and lowering of postprandial hyperglycemia, resulting in improved glycemic control.

Because its mechanism of action is different, the effect of acarbose in enhancing glycemic control is additive to that of sulfonylureas, metformin or insulin when used in combination. In addition, acarbose diminishes the insulinotropic and weight-increasing effects of sulfonylureas.

Acarbose has no inhibitory activity against lactase and consequently does not induce lactose intolerance.

Pharmacokinetics

Absorption

One to 2% of an oral dose of acarbose is absorbed from the gastrointestinal tract as unchanged drug. When ^{14}C-labelled acarbose was administered orally, approximately 35% of the total radioactivity (changed and unchanged drug) was absorbed. An average of 51% of an oral dose was excreted in the feces as unabsorbed drug-related radioactivity within 96 hours of ingestion. Because acarbose acts locally within the gastrointestinal tract, this low systemic bioavailability of parent compound is therapeutically desired. Following oral dosing of healthy volunteers with ^{14}C-labelled acarbose, peak plasma concentrations of radioactivity were attained 14-24 hours after dosing, while peak plasma concentrations of active drug were attained at approximately 1 hour. The delayed absorption of acarbose-related radioactivity reflects the absorption of metabolites that may be formed by either intestinal bacteria or intestinal enzymatic hydrolysis.

Distribution

Only 1-2% of an oral dose of acarbose is absorbed into the central circulation.

Metabolism

Acarbose is metabolized exclusively within the gastrointestinal tract, principally by intestinal bacteria, but also by digestive enzymes. A fraction of these metabolites (approximately 34% of the dose) is absorbed and subsequently excreted in the urine. At least 13 metabolites have been separated chromatographically from urine specimens. The major metabolites have been identified as 4-methylpyrogallol derivatives (ie, sulfate, methyl, and glucuronide conjugates). One metabolite (formed by cleavage of a glucose molecule from acarbose) also has α-

glucosidase inhibitory activity. This metabolite, together with the parent compound, recovered from the urine, accounts for less than 2% of the total administered dose.

Excretion

The fraction of acarbose that is absorbed as intact drug is almost completely excreted by the kidneys. When acarbose was given intravenously, 89% of the dose was recovered in the urine as active drug within 48 hours. In contrast, less than 2% of an oral dose was recovered in the urine as active (ie, parent compound and active metabolite) drug. This is consistent with the low bioavailability of the parent drug. The plasma elimination half-life of acarbose activity is approximately 2 hours in healthy volunteers. Consequently, drug accumulation does not occur with three times a day (t.i.d.) oral dosing.

Special Populations and Conditions

Renal Insufficiency

Patients with severe renal impairment (creatinine clearance < 25 mL/min/1.73m^2) attained about 5 times higher peak plasma concentrations of acarbose and 6 times larger AUCs than volunteers with normal renal function.

STORAGE AND STABILITY

Storage should be between 15°C and 25°C.

At storage conditions up to 25°C and below 60% relative humidity, the unpacked tablets can be stored for up to two weeks. At higher temperatures and/or relative humidity, discoloration can occur in tablets that are not in the pack. The tablets should therefore not be removed from the foil until immediately before use.

DOSAGE FORMS, COMPOSITION AND PACKAGING

GLUCOBAY tablets contain 50 or 100 mg of acarbose.

Nonmedicinal ingredients: corn starch, microcrystalline cellulose, silicon dioxide, magnesium stearate.

The formulation contains no preservatives or coloring agents.

GLUCOBAY 50 and 100 mg tablets are available in blister packs in cartons of 120 tablets.

Tablets are round and white to yellow-tinged in color. The 50 mg tablet has a 7 mm diameter and 10 mm radius of curvature; it is scored and marked with "G50" on one side and the Bayer cross on the other. The 100 mg tablet has a 9 mm diameter and 15 mm radius of curvature; it is scored and marked with "G100" on one side and the Bayer cross on the other.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Acarbose is an oligosaccharide. It contains acarviosine, an unsaturated cyclitol unit linked to an amino sugar, bonded to a maltose unit.

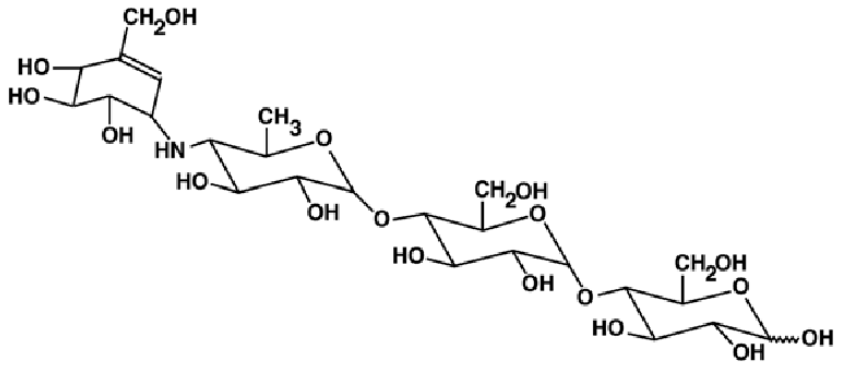
Proper name: Acarbose

Chemical name: O-4,6-dideoxy-4-[[(1S, 4R, 5S, 6S)-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl]amino]-α-D-glucopyranosyl-(1→4)-O-α-D-glucopyranosyl-(1→4)-D-glucose

Molecular formula: $C_{25}H_{43}NO_{18}$

Molecular weight: 645.6

Structural formula:



Physicochemical properties: Acarbose is a white to off-white powder. It remains stable for several hours in dilute acid (0.1M HCl), alkali (0.1M NaOH), at pH 7 and at body temperature (37-40°C). Acarbose is soluble in water and has a pKa of 5.1. The solubility of acarbose in water is approximately 140g/100 mL at 20°C.

CLINICAL TRIALS

Clinical Experience in Type 2 Diabetes Mellitus Patients on Monotherapy, or in Combination with Sulfonylureas, Metformin or Insulin

GLUCOBAY™ (acarbose) was studied as monotherapy and as combination therapy to sulfonylurea, metformin, or insulin treatment. (2-19) The treatment effects on HbA1c levels and one-hour postprandial glucose levels are summarized in Table 3 and Table 4, respectively, for four placebo-controlled, double-blind, randomised studies conducted in the United States. The placebo-subtracted treatment differences, which are summarized below, were statistically significant for both variables in all of these studies.

Study 1 (n=109) involved patients on background treatment with diet only. The mean effect of the addition of GLUCOBAY to diet therapy was a change in HbA1c of -0.0078 (-0.78%), and an improvement of one-hour postprandial glucose of -4.13 mmol/L. (6)

In Study 2 (n=137), the mean effect of the addition of GLUCOBAY to maximum sulfonylurea therapy was a change in HbA1c of -0.0054 (-0.54%), and an improvement of one-hour postprandial glucose of -1.86 mmol/L.

In Study 3 (n=147), the mean effect of the addition of GLUCOBAY to maximum metformin therapy was a change in HbA1c of -0.0065 (-0.65%), and an improvement of one-hour postprandial glucose of -1.91 mmol/L. (20)

Study 4 (n=145) demonstrated that GLUCOBAY added to patients on background treatment with insulin resulted in a mean change in HbA1c of -0.0069 (-0.69%), and an improvement of one-hour post prandial glucose of -2.00 mmol/L. (21)

A one year study of GLUCOBAY as monotherapy or in combination with sulfonylurea, metformin or insulin treatment was conducted in Canada in which 316 patients were included in the primary efficacy analysis (Figure 1). In the diet, sulfonylurea and metformin groups, the mean decrease in HbA1c produced by the addition of GLUCOBAY was statistically significant at six months. In the GLUCOBAY treated patients on insulin, there was a statistically significant reduction in HbA1c at six months. (3)

Table 3 – Effect of GLUCOBAY on HbA1c

Study	Treatment	HbA1c[a]			*P*-Value
		Mean Baseline	Mean Change from Baseline[b]	Treatment Difference	
Study 1 (6)	Placebo Plus Diet	0.0867	+0.0033	—	—
	GLUCOBAY 100 mg t.i.d. Plus Diet	0.0869	-0.0045	-0.0078	0.0001
Study 2	Placebo Plus SFU[c]	0.0956	+0.0024	—	—
	GLUCOBAY 50-300 mg t.i.d. Plus SFU[c]	0.0964	-0.0030	-0.0054	0.0096
Study 3 (20)	Placebo Plus Metformin[d]	0.0817	+0.0008	—	—
	GLUCOBAY 50-100 mg t.i.d. Plus Metformin[d]	0.0846	-0.0057[f]	-0.0065	0.0001
Study 4 (21)	Placebo Plus Insulin[e]	0.0869	+0.0011	—	—
	GLUCOBAY 50-100 mg t.i.d. Plus Insulin[e]	0.0877	-0.0058	-0.0069	0.0001

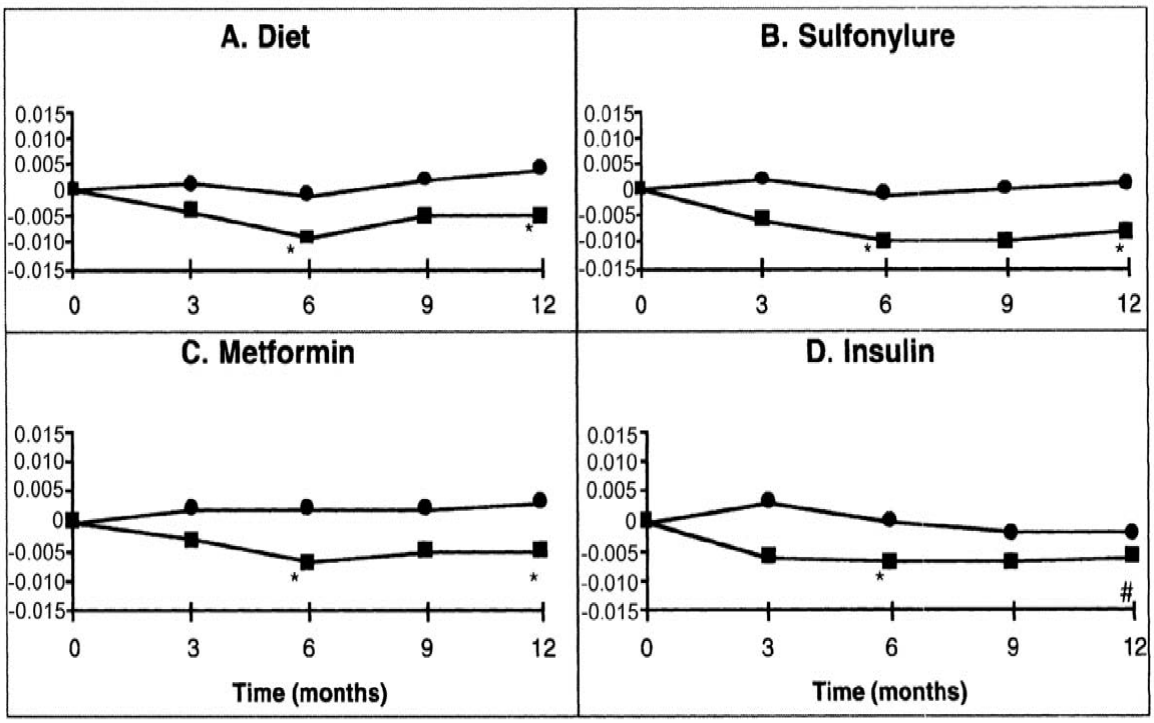
a HbA1c Normal Range:0.0046
b After four months treatment in Study 1, and six months in Studies 2, 3, and 4
c SFU, sulfonylurea, maximum dose
d Metformin dosed at 2000 mg/day or 2500 mg/day
e Mean dose of insulin 61 U/day
f Results are adjusted to a common baseline of 0.0833

Table 4 – Effect of GLUCOBAY on Postprandial Glucose

Study	Treatment	One-Hour Postprandial Glucose (mmol/L)			*P*-Value
		Mean Baseline	Mean Change from Baseline[a]	Treatment Difference	
Study 1 (6)	Placebo Plus Diet	16.51	+1.77	—	—
	GLUCOBAY 100 mg t.i.d. Plus Diet	16.62	-2.37	-4.13	0.0001
Study 2	Placebo Plus SFU[b]	17.14	+0.344	—	—
	GLUCOBAY 50-300 mg t.i.d. Plus SFU[b]	17.28	-1.52	-1.86	0.0017
Study 3 (20)	Placebo Plus Metformin[c]	14.66	+0.183[e]	—	—
	GLUCOBAY 50-100 mg t.i.d. Plus Metformin[c]	15.72	-1.72[e]	-1.91	0.0001
Study 4 (21)	Placebo Plus Insulin[d]	15.51	+0.444	—	—
	GLUCOBAY 50-100 mg t.i.d. Plus Insulin[d]	15.43	-1.56	-2.00	0.0178

a After four months treatment in Study 1, and six months in Studies 2, 3, and 4
b SFU, sulfonylurea, maximum dose
c Metformin dosed at 2000 mg/day or 2500 mg/day
d Mean dose of insulin 61 U/day
e Results are adjusted to a common baseline of 15.2 mmol/L

Figure 1 – Effect of GLUCOBAY on Mean Change in HbA1c Levels from Baseline



Effects of GLUCOBAY (■) and Placebo (●) on mean change in HbA1c levels from baseline throughout a one year study in patients with type 2 diabetes mellitus when used in combination with: (A) diet alone; (B) sulfonylurea; (C) metformin; or (D) insulin. Treatment differences at 6 and 12 months were tested: *P<0.01; #P=0.077. (3)

DETAILED PHARMACOLOGY

In Vitro Enzyme Inhibition

Acarbose (3 mM) competitively inhibited the activity of glucoamylase by 82%, sucrase by 68%, and maltase by 31%. No effect on lactase and trehalose activity was observed.

Effects on Carbohydrate Absorption

Addition of acarbose to perfusion fluid containing radiolabelled sucrose or maltose resulted in a dose-dependent inhibition of absorption of these disaccharides from in situ perfused jejunal loops of rats.

The carbohydrate content of the stomach, and small and large intestines of rats after they had received a carbohydrate load with or without acarbose was examined. Absorption of the carbohydrate load was delayed in the acarbose-treated animals. After oral administration of acarbose (0.16 to 0.63 mg) with 500 mg sucrose, the passage of sucrose through the stomach into the small intestine was unaffected; however, a dose-dependent increase was found in the amount

of undigested carbohydrate detected in the small intestine 15 to 240 minutes later. In loading tests with starch (300 mg), a dose dependent larger amount of undigested carbohydrate was found in the small intestine after 2 and 4 hours. Similarly, 4 hours after starch loading, a larger amount of undigested carbohydrate was found in the large intestine of animals treated with acarbose. This suggests that the degradation of starch, as well as sucrose, is inhibited by acarbose. Studies in rats which had been fed radiolabelled sucrose with and without acarbose provided additional support that acarbose inhibits the degradation of sucrose in the gastrointestinal tract.

It has been demonstrated that acarbose is not effective in altering the postprandial blood glucose rise associated with the administration of monosaccharides. Fasting rats were given either 2.5 g/kg glucose or 1.25 g/kg glucose +1.25 g/kg fructose with or without acarbose, orally. The resulting postprandial blood glucose rise was unaffected in the presence of acarbose compared to control, even at levels of 25 mg/kg. In addition, administration of acarbose intravenously (7.5 mg/kg) along with administration of sucrose (2.5 g/kg) orally did not effect any reduction in blood glucose rise.

Effects on Blood Glucose Levels

The pharmacological effect of acarbose was investigated using postprandial blood glucose rise as a measure of efficacy. The amount of acarbose required to reduce the postprandial blood glucose rise by 50% (ED_{50}) after various carbohydrate loads was determined for rats and mice. Summary results are represented in Table 5, below.

Table 5 – Effect of Acarbose on Postprandial Glucose in Animal Studies

Species	Carbohydrate Load	ED_{50}
Mouse	raw starch (2 g/kg)	0.5 mg/kg
	cooked starch (1 g/kg)	1.7 mg/kg
	sucrose (2 g/kg)	1.5 mg/kg
Rat	cooked starch (1 g/kg)	1.5 mg/kg
	sucrose (2.5 g/kg)	1.1 mg/kg
	starch (1 g/kg) + sucrose (1.5 g/kg)	2.3 mg/kg
	maltose (1 g/kg)	ca 12 mg/kg

In all species tested, acarbose exerts its activity in the intestinal tract. The action of acarbose is based on inhibition of the intestinal enzymes (α-glucosidases) involved in the degradation of disaccharides, oligosaccharides and polysaccharides. This leads to a dose-dependent delay in the digestion of these carbohydrates. Most importantly, glucose derived from carbohydrates is released and taken up into the blood more slowly. In this way, acarbose reduces the postprandial rise in blood glucose. As a result of the balancing effect on the uptake of glucose from the intestine, the blood glucose fluctuations over the day are reduced and the mean blood glucose values decrease. (21)

Effects on Plasma Insulin

The effect of acarbose on postprandial plasma insulin levels was examined in a number of studies. In a sucrose (2.5 g/kg) loading test in fasted, normal rats, acarbose (1.5 mg/kg) caused significant decreases in the postprandial insulin rise. Reductions in postprandial insulin rise were also observed after loading with cooked starch (1.0 g/kg) + sucrose (1.5 g/kg), or beer (40 mL/kg) and treatment with acarbose (2.3 mg/kg). Similarly, after loading with casein (1.0 g/kg) and sucrose (1.0 g/kg), acarbose (0.78, 1.6, 3.1 mg/kg) dose dependently reduced both postprandial glucose and insulin levels compared to controls.

Effects on Oral Hypoglycemic Agents

In the rat, concomitant oral administration of acarbose (120-170 mg/kg daily) resulted in mild to moderate reduction in exposure to chlorpropamide, glibenclamide and metformin. This same effect was not observed in humans (see **DRUG INTERACTIONS - Drug-Drug Interactions**).

Other Pharmacological Effects

Acarbose had no cardiovascular, hemodynamic, renal or neurological effects.

Gastrointestinal changes were not observed in electron microscopic studies of the small intestine of acarbose treated rats.

Adaptive caecal enlargement occurred in rats as a result of the pharmacodynamic effect of acarbose. Caecal enlargement has been observed in rats fed with slowly digestible and fermentable carbohydrates (several starches, lactulose and beta-cyclodextrin).

TOXICOLOGY

Acute Toxicity

Results of acute toxicity testing are summarized in the following table:

Table 6 – Effect of Acarbose on Postprandial Glucose in Animal Studies

Species	Sex	Route of Application	LD_{50} (g/kg)
Mouse	Male	per os	>15.4
Mouse	Male	intravenous	>7.7
Rat	Male	per os	>15.4
Rat	Male	intravenous	7.4
Rat	Female	intravenous	5.5
Dog	Male & Female	per os	>10.0
Dog	Male & Female	intravenous	>3.8

Based on these results, acarbose may be characterized as practically nontoxic after single oral doses; LD_{50} could not be determined. The substance also has low toxicity when administered intravenously.

Repeated Dose Toxicity

General

An extensive programme of chronic toxicity studies has been carried out with acarbose. There have been 9 animal studies (hamsters [2], Sprague-Dawley rats [4], Wistar rats [2] and Beagle dogs [1]) over periods of 52 weeks (dogs) to 30 months (rats). All of the chronic rat studies included an interim sacrifice at either 12 or 14 months. In an early study in Sprague-Dawley rats there was evidence of significant effects of acarbose on weight development. It was suspected that there was a possible effect of a nutritional derangement on the tumour profile of the treated animals in the study. As a result, an additional study was carried out with a glucose "supplement" in the animals' diet. Such a study was also carried out in hamsters. The design of both the studies was similar, with two control groups, one receiving no glucose and one which did receive glucose; all the acarbose treated animals received the glucose supplement.

General Health of Animals During Study

Appearance and behaviour of rats treated with doses of up to 4500 ppm of feed (corresponding to 300 to 500 mg/kg) was generally no different from that of animals in the control groups. Beagle dogs treated with doses up to 400 mg/kg did exhibit some symptoms of toxicity; there were three incidences of vomiting and several of sedation; almost all acarbose treated animals exhibited pale gums between weeks 12 and 28 of the study.

Food and Water Intake, Body Weight Development

In studies with hamsters and dogs, there were no significant differences from control in food and water intake and in weight gain. The studies carried out in both species of rats, did indicate more widespread effects on food and water intake, with some studies in Sprague-Dawley rats showing effects in all dose groups. The effects were less evident in studies in Wistar rats; they were gender specific or only at higher doses. Body weight gain was generally retarded in Sprague-Dawley rats, although in animals administered a glucose solution supplement, the effect was only seen in males at the highest dose (ca 250 mg/kg/day) and in females at doses of 70 mg/kg/day and upwards. Wistar rats administered acarbose in feed exhibited retarded growth at doses of 30 mg/kg/day and up, while those receiving acarbose by gavage developed normally (compared to control).

The effects on food intake and body weight seen were concluded to be as a result of the pharmacological effect of the drug, and were improved by increased caloric intake (glucose supplement in rats).

Mortality

In general, mortality in the treated animals was either comparable to that in the control animals, or, in some cases mortality was actually lower (in some cases significantly) in the treated animals. In the Beagle dog study, mortality was higher in the highest dose group (400 mg/kg, ♀, in that the only death which occurred during the study was in this group. The death occurred on the 123rd day of the study, following several days of severe sedation which increased to cachexia.

Enzyme Effects

In long-term toxicity studies some instances of statistically significant changes in clinical chemistry parameters were observed: decreased α-amylase activity, increased alkaline phosphatase levels, and increased levels of SGOT and/or SGPT.

Treatment-related decreases in **α-amylase** activity were seen in one study in rats, and in both of the studies in dogs. In Wistar rats, urinary levels of α-amylase were significantly reduced in the 150 and 450 mg/kg dose groups, while blood and pancreas levels were unaffected. In dogs, serum α-amylase levels were reduced at doses above 50 mg/kg in males and 150 mg/kg in females. In addition, there was decreased α-amylase activity in the pancreas of all treated animals at the end of study. Reduced glucosidase values are believed to be a direct result of the pharmacodynamic effect of acarbose and component 2.

Elevations in **alkaline phosphatase (AP)** were more common; they were observed in the majority of the studies in rats and dogs. Rats treated with 4500 ppm (corresponding to 300-500 mg/kg) of acarbose in feed for 2 to 24 months exhibited increased AP levels. A decline of the elevated serum levels to normal values was observed in 7 days either when the standard diet was replaced by a low carbohydrate diet or when acarbose was eliminated from the standard feed.

Separation of the isoenzymes in the serum indicated that the elevated AP levels were not caused by an increase in liver AP activity. In the wall of the upper small intestine, the AP activity was approximately 30 to 50 times that in the liver. The highest AP activity was found in kidney tissue. Decreases in elevated intestinal or renal AP activities were observed either when acarbose was administered by gavage rather than administered in standard feed or when the standard feed was replaced by a low carbohydrate diet.

Levels of SGOT, SGPT and bilirubin were significantly increased in rats receiving acarbose in their standard feed. When their feed was replaced with a low carbohydrate diet, SGOT, SGPT and bilirubin levels were no different from controls.

In studies where treatment-related effects on enzyme values for α-amylase and alkaline phosphatase in the plasma were evident, there was no indication of damage to the liver or the intestinal epithelia.

Carcinogenicity

Nine carcinogenicity studies were conducted in three animal species (rat, hamster, dog) including two rat strains (Sprague-Dawley and Wistar).

In the first rat study, Sprague-Dawley rats received acarbose in feed at high doses (up to approximately 500 mg/kg body weight) for 104 weeks. Acarbose treatment resulted in a significant increase in the incidence of renal tumors (adenomas and adenocarcinomas) and benign Leydig cell tumors. This study was repeated with a similar outcome. Further studies were performed to separate direct carcinogenic effects of acarbose from indirect effects resulting from the carbohydrate malnutrition induced by the large doses of acarbose employed in the studies. In one study using Sprague-Dawley rats, acarbose was mixed with feed but carbohydrate deprivation was prevented by the addition of glucose to the diet. In a 26-month study of Sprague-Dawley rats, acarbose was administered by daily postprandial gavage so as to avoid the pharmacologic effects of the drug. In both of these studies, the increased incidence of renal tumors found in the original studies did not occur. Acarbose was also given in food and by postprandial gavage in two separate studies in Wistar rats. No increased incidence of renal tumors was found in either of these Wistar rat studies. In two feeding studies of hamsters, with and without glucose supplementation, there was also no evidence of carcinogenicity.

Reproductive Toxicology

A number of studies were carried out to investigate fertility performance, embryotoxicity, teratogenicity, perinatal and postnatal effects.

Treatment of male and female rats (60 and 21 days respectively pre-mating) at oral doses of up to 540 mg/kg failed to show any effect on the general reproductive function of either the parents or the F_1 generation.

Investigations were carried out on the rat and the rabbit at doses of up to 480 mg/kg. No teratogenic effects were evident in either species; no embryotoxic effects were evident in rats. However, at the highest dose of 480 mg/kg, rabbit dams did exhibit some gastrointestinal effects likely due to the pharmacologic action of the drug which resulted in undigested carbohydrates in dams' colons. This group had a lower mean number of foetuses than the control group. The investigators concluded that acarbose was not embryotoxic in rabbits at doses up to 150 mg/kg, but at 480 mg/kg it caused some embryolethal effects which correlated with adverse effects seen in the dams.

Female rats were treated with doses of up to 540 mg/kg/day from Day 16 of gestation until 4 weeks after delivery. Overall, pre- and postnatal development did not differ significantly from control.

Acarbose is not teratogenic and does not adversely affect reproductive function at the doses studied.

Mutagenesis

Acarbose showed no mutagenic activity in six in vitro and three in vivo assays.

A series of nine tests were carried out to examine the potential genotoxicity of acarbose. There is no evidence of genotoxicity of acarbose.

The UDS assay indicated no damage caused by acarbose at concentrations of up to 400 µL. No DNA binding of acarbose to liver or kidney tissue was detected.

At concentrations of up to 2500 µg/plate, no indication of point mutational effects was found in the Salmonella/microsome test. In the adult rat liver epithelial cell/hypoxanthine-guanine phosphoribosyl transferase mutagenesis (ARL/HGPRT) assay, no cytotoxic effect was found at doses up to 500 µg/L. Samples of urine from patients who had received treatment with acarbose were tested for point mutagenic activity. No effect was seen at doses of up to 500 µL per plate.

The micronucleus test, dominant lethal test and Chinese hamster CHO chromosome test all failed to show any damaging effect of acarbose, at doses of up to 500 mg/kg, 2000 mg/kg and 32 mM respectively. Further investigations on the lymphocytes of exposed subjects were also negative.

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PART III: CONSUMER INFORMATION

PrGLUCOBAY™

acarbose

This leaflet is Part 3 of a three-part "Product Monograph" published when GLUCOBAY was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about GLUCOBAY. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

GLUCOBAY (acarbose) is used alone or in combination with a sulfonylurea (such as tolbutamide, chlorpropamide, or DiaBeta®/glyburide), metformin, or insulin to lower blood glucose in adult patients with type 2 diabetes mellitus in addition to proper diet, exercise and weight reduction.

What it does:

GLUCOBAY will slow the absorption of glucose from your gut to reduce the high blood glucose levels that occur after each meal.

When it should not be used:

Do not take GLUCOBAY if you have or have had any of the following:

- Allergic reaction to acarbose or any of the other ingredients in GLUCOBAY
- Inflammation or ulceration of the bowel (eg, ulcerative colitis or Crohn's disease)
- Diabetic ketoacidosis
- Bowel obstruction
- Chronic intestinal diseases that affect digestion or absorption of food, or a large hernia

What the medicinal ingredient is:

Acarbose

What the important nonmedicinal ingredients are:

corn starch, magnesium stearate, microcrystalline cellulose, silicon dioxide

What dosage forms it comes in:

Tablets. Each tablet contains 50 mg or 100 mg acarbose.

WARNINGS AND PRECAUTIONS

GLUCOBAY in combination with a sulfonylurea or insulin may cause low blood sugar (hypoglycemia). You should ask your doctor, pharmacist or diabetes educator about the symptoms of low blood sugar and what to do if you experience these symptoms. You should also test your blood sugar according to instructions given to you by your doctor, nurse, or pharmacist.

Before you use GLUCOBAY talk to your doctor or pharmacist if:

- you have or have had kidney or liver disease
- you are pregnant or planning to get pregnant
- you are breast-feeding

GLUCOBAY is not recommended for use in children under 18 years of age.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including the medicine you can buy without a prescription, and natural health products.

Drugs that interact with GLUCOBAY include digestive enzyme preparations, cholestyramine, diuretics (water pills), corticosteroids (such as prednisone), digoxin, thyroid medications, estrogen, oral contraceptives, phenytoin, nicotinic acid, sympathominetics, and isoniazid.

Avoid drinking alcohol while taking GLUCOBAY.

PROPER USE OF THIS MEDICATION

Take the tablets as prescribed by your doctor. Tablets should be taken orally with the first bite of a main meal. Do not take GLUCOBAY between meals.

You should continue to monitor your blood glucose levels according to the instructions given to you by your healthcare professional.

Usual dose

The usual starting dose is 50 mg once daily. The usual maintenance dose is 50 mg or 100 mg three times daily. The maximum dose is 100 mg three times daily.

Overdose

If you take more GLUCOBAY tablets than you should, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose

If you miss a dose, take your next dose as usual. Do not double dose to make up for the missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

You may experience some side effects while taking GLUCOBAY. The most common are gastrointestinal in nature, such as flatulence (gas) and abdominal discomfort. It is also possible that you may pass softer stools or even experience diarrhea, particularly after a meal containing foods with sucrose (ordinary sugar). Normally, these symptoms will diminish with continued treatment. You should not take antacid preparations for treating these symptoms, as they are unlikely to have any beneficial effects. If your symptoms persist, or if you have any other undesirable effects, consult your doctor.

GLUCOBAY, when given alone, should not cause hypoglycemia (low blood sugar). However, since sulfonylureas (oral antidiabetic drugs) or insulin may cause hypoglycemia, the combination of a sulfonylurea or insulin and GLUCOBAY may also cause hypoglycemia. If you do experience hypoglycemia while you are taking GLUCOBAY, either alone or with a sulfonylurea, metformin or insulin, do not treat it with ordinary sugar (sucrose); instead, take glucose tablets (also known as dextrose).

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/ Effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Uncommon			
Nausea, vomiting, abdominal pain	T		
Rare			
Edema (swelling)	T		
Jaundice (yellowing of the skin)			T
Very Rare			
Allergic reactions: rash, skin inflammation		T	

This is not a complete list of side effects. For any unexpected effects while taking GLUCOBAY, contact your doctor or pharmacist.

HOW TO STORE IT

It is best if you keep your tablets in their original carton. The tablets should be kept in a dry place at a temperature between 15°C and 25°C.

Keep out of the reach of children.

Do not use the tablets beyond the expiry date.

REPORTING SUSPECTED SIDE EFFECTS

Canada Vigilance Program

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effect, please contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your health professional or pharmacist first, or Bayer Medical Information at 1-800-265-7382 or canada.medinfo@bayer.com.

This document plus the full product monograph, prepared for health professionals can be found at: www.bayer.ca or by contacting the manufacturer at the above mentioned phone number and email address.

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