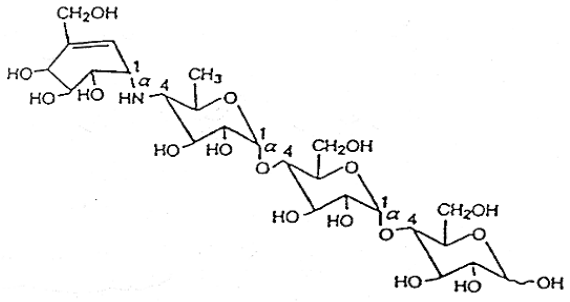
PRODUCT INFORMATION

GLYBOSAY TABLETS
(acarbose)

NAME OF THE MEDICINE

GLYBOSAY contains acarbose (CAS number 56180-94-0) which is a complex oligosaccharide of microbial origin. Acarbose is made up of an unsaturated cyclitol unit, an amino sugar and a maltose residue. Acarbose is a white or yellowish powder with a molecular weight of 645.6. Acarbose is very soluble in water and has a pKa of 5.1. The empirical formula is $C_{25}H_{43}NO_{18}$ and the chemical structure is shown below:



DESCRIPTION

In addition to acarbose, GLYBOSAY tablets contain the following inactive ingredients: microcrystalline cellulose, pregelatinised maize starch, colloidal anhydrous silica and magnesium stearate.

PHARMACOLOGY

Pharmacokinetics

Absorption: One to 2% of an oral dose of acarbose is absorbed from the gastrointestinal tract as unchanged drug. After the oral administration of 200 mg ^{14}C-labelled acarbose (200 mg) to 6 healthy volunteers, approximately 35% of total radioactivity (changed and unchanged drug) appeared in the urine. An average of 51% of the oral dose was excreted in the faeces as unabsorbed drug-related radioactivity within 96 hours of ingestion. The proportion of active substance excreted in the urine was 1.7% of the administered dose. The low systemic bioavailability of the parent drug is therapeutically desired, because acarbose acts locally within the gastrointestinal tract. Following oral dosing with acarbose, peak plasma concentrations of radioactivity were attained 14 - 24 hours after dosing (586.3 ± 282.7 µg/L after 20.7 ± 5.2 hours), while peak plasma concentrations of active drug were attained at approximately 1 hour (52.2 ± 15.7 µg/L after 1.1 ± 0.3 hours). The delayed absorption of acarbose-related radioactivity reflects the absorption of metabolites that may be formed by either intestinal bacteria or intestinal enzymatic hydrolysis.

Metabolism: Acarbose is metabolised exclusively within the gastrointestinal tract, principally by intestinal bacteria, but also by digestive enzymes. A fraction of these metabolites (approximately 34% of the dose) was 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 the 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.

Elimination: 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.

Mechanism of Action
Acarbose exerts its activity in the intestinal tract. In contrast to sulfonylureas, it has no stimulatory action on the pancreas.

The action of acarbose depends on an inhibition of intestinal enzymes (alpha-glucosidases) involved in the degradation of ingested disaccharides, oligosaccharides, and polysaccharides, but not monosaccharides. Maximal specific inhibitory activity is against sucrase. This leads, dose dependently, to a delayed digestion of the above carbohydrates. The result is that absorbable monosaccharides (dextrose) originating from carbohydrates are released more slowly and hence more slowly taken up into blood. Absorption of monosaccharides is not affected. In this way, acarbose reduces the postprandial rise in blood glucose, the blood-glucose fluctuations in the course of the day become truncated, and the mean blood-glucose level is reduced. Acarbose lowers abnormally high levels of glycosylated haemoglobin.

CLINICAL TRIALS

Clinical Experience in Non-Insulin Dependent Diabetes Mellitus (NIDDM) Patients on Dietary Treatment Only: Results from six controlled, fixed-dose, monotherapy studies of acarbose in the treatment of NIDDM, involving 769 acarbose-treated patients, were combined and a weighted average of the difference from placebo in the mean change from baseline in glycosylated haemoglobin (HbA_{1c}) was calculated for each dose level as presented below.

Table 1

Mean change in HbA_{1c} in Fixed-Dose Monotherapy Studies			
Dose of Acarbose*	**N**	**Change in HbA_{1c} %**	**p-Value**
25 mg t.i.d.	110	-0.44	0.0307
50 mg t.i.d.	131	-0.77	0.0001
100 mg t.i.d.	244	-0.74	0.0001
200 mg t.i.d.**	231	-0.86	0.0001
300 mg t.i.d.**	53	-1.00	0.0001

*Acarbose was statistically significantly different from placebo at all doses. Although there were no statistically significant differences among the mean results for doses ranging between 50 to 300 mg t.i.d. some patients may derive benefit by increasing the dosage from 50 to 100 mg t.i.d.
**Although studies utilised a maximum dose of 200 or 300 mg t.i.d. the maximum recommended dose for patients is 200 mg t.i.d.

Clinical Experience in NIDDM Patients Receiving Sulfonylureas: Acarbose was studied as adjunctive therapy to sulfonylurea treatment in two large, placebo-controlled, double-blind, randomised studies of 24 weeks duration, in which 540 patients were included in the efficacy analysis. In addition, acarbose was studied as adjunctive therapy to sulfonylurea treatment in a third study of one year duration, in which patients were stratified according to background therapy. Study 1 (Table 2) involved patients under treatment at entry with diet alone who were subsequently randomised to four treatment groups. At the end of the study, patients in the acarbose + tolbutamide group showed a mean treatment effect on glycosylated haemoglobin (HbA_{1c}) of -1.78% and were receiving a significantly lower mean daily dose of tolbutamide than patients in the tolbutamide-alone group. Also, the efficacy in the acarbose + tolbutamide groups was significantly better than in the other three treatment groups. Study 2 (Table 2) involved patients taking background treatment with maximum daily doses of sulfonylureas. At the end of this study, the mean effect of the addition of acarbose to maximum sulfonylurea therapy was a change in HbA_{1c} of -0.54%. In addition, there was a significantly greater proportion of patients in the acarbose + sulfonylurea group who reduced their sulfonylurea dose as compared to patients in the placebo + sulfonylurea group. In Study 3 (Table 2), the addition of acarbose to a background treatment of sulfonylurea in 96 patients produced an additional change in mean HbA_{1c} of -0.9%.

Table 2

Study	Treatment	HbA_{1c} (%)			p-Value
		Mean Baseline*	Mean Change from Baseline	Treatment Difference** (90% Confidence Interval)	
1	Placebo	9.48	+0.05	-	-
	Acarbose 200† mg t.i.d.	9.19	-0.71	-0.76 (-1.05, -0.47)	0.0005
	Tolbutamide 250-1000 mg t.i.d. (mean dose 2.4 g/d)	9.28	-1.22	-1.27 (-1.56, -0.98)	0.0001
	Acarbose 200† mg t.i.d. + Tolbutamide 250-1000 mg t.i.d. (mean dose 1.9 g/d)	8.99	-1.73	-1.78 (-2.08, -1.48)	0.0001
2	Sulfonylurea + Placebo	9.56	+0.24	-	-
	Sulfonylurea + Acarbose 50-300† mg t.i.d.	9.64	-0.30	-0.54 (-0.83, -0.25)	0.0096
3	Sulfonylurea + Placebo	8.00	+0.10	-	-
	Sulfonylurea + Acarbose 50-200† mg t.i.d.	8.10	-0.80	-0.90 (-1.33, -0.47)	0.0020
	Metformin + Placebo	7.9	+0.3	-	-
	Metformin + Acarbose 50-200† mg t.i.d.	7.8	-0.5	-0.8 (-1.30, -0.30)	0.0106

* Normal range: 4-6%
** The result of subtracting the placebo group average.
† Although studies utilised a maximum dose of 200 or 300 mg t.i.d., the maximum recommended dose for patients is 200 mg t.i.d.

Clinical Experience in NIDDM Patients Receiving Metformin: Acarbose was also studied as adjunctive therapy to metformin treatment in a one year study (Study 3). In this study (Table 2), the addition of acarbose to 74 patients on metformin treatment produced an additional change in mean HbA_{1c} of -0.8%.

As can be seen by the above studies, acarbose lowers HbA_{1c} levels either alone or in combination with other oral hypoglycaemic agents. Overall 58% of the NIDDM patients studied were women. There is no long-term data on morbidity and mortality.

INDICATIONS

As an adjunct to prescribed diet and exercise for the management of blood glucose concentrations in non-insulin dependent diabetic patients who are inadequately controlled by diet alone or by diet and oral hypoglycaemic agents.

CONTRAINDICATIONS

Hypersensitivity to acarbose and/or any of the inactive tablet constituents, pregnancy and lactation.

Acarbose should not be used in patients under 18 years of age.

Acarbose is contraindicated in patients with severe renal impairment (creatinine clearance <25 mL/min).

Acarbose should not be used in patients with gastrointestinal disorders associated with malabsorption. It should not be used in patients with inflammatory bowel disease, such as ulcerative colitis and Crohn's disease.

Acarbose should not be used in patients with partial intestinal obstruction, or in patients predisposed to intestinal obstruction or ileus.

Similarly, Acarbose should not be used in conditions that could be aggravated by an increased formation of intestinal gas (e.g. Roemhelds syndrome, major hernias, intestinal obstruction and intestinal ulcers).

PRECAUTIONS

General

Ingestion of sucrose and food that contains sucrose can easily lead to considerable intestinal symptoms (e.g. flatulence and bloating), or even diarrhoea during treatment with acarbose, as a result of increased carbohydrate fermentation in the colon (see **ADVERSE EFFECTS**).

Hypoglycaemia: Acarbose has an antihyperglycaemic effect, but does not itself induce hypoglycaemia. If acarbose is prescribed in addition to drugs containing sulfonylureas or metformin or in addition to insulin, a fall of blood glucose levels into the hypoglycaemic range may necessitate a suitable decrease in the sulfonylurea, metformin or insulin dose. In individual cases hypoglycaemic shock may occur. In the event of acute hypoglycaemia, it should be borne in mind that cane sugar (sucrose) is broken down into fructose and glucose more slowly during acarbose treatment and is therefore unsuitable for a rapid elimination of hypoglycaemic phenomena. Glucose (i.e. dextrose) should be used in place of cane sugar (sucrose).

***Elevated Serum Transaminase Levels*:** In clinical trials at doses of 50 mg t.i.d. and 100 mg t.i.d., the incidence of serum transaminase elevations with acarbose was the same as placebo. In long-term studies (up to 12 months, and including acarbose doses up to 300 mg t.i.d.) conducted in the U.S., treatment-emergent elevations of serum transaminases (ALT and/or AST) occurred in 15% of acarbose-treated patients as compared to 7% of placebo-treated patients. The elevations were asymptomatic, reversible, more common in females and in general, were not associated with other evidence of liver dysfunction.

Patients' liver enzyme values should be monitored regularly, preferably at monthly intervals for the first 6 to 12 months after initiation of acarbose therapy. If elevated transaminases are observed, a reduction in dosage or withdrawal of therapy may be warranted, particularly if the elevations persist. In such circumstances, patients should be monitored at weekly intervals

until normal values are established.

Effects on Fertility
Fertility studies in rats after oral administration produced no untoward effect on fertility or on the overall capacity to reproduce at oral dose levels of 540 mg/kg/day (approximately half the exposure at the maximal therapeutic dose based on the AUC in rats).

Use in Pregnancy (Category B3)
Studies in rats and rabbits have not yielded any evidence of teratogenic or embryotoxic effects due to acarbose when administered at oral doses up to 540 and 480 mg/kg/day, respectively (approximately half the exposure at the maximal therapeutic dose based on the AUC in rats). At oral doses of 480 mg/kg/day, acarbose caused resorptions in rabbits and increased prenatal losses in rats during organogenesis, but was not teratogenic. There are, however, no adequate and well-controlled studies in pregnant women.

Acarbose should not be administered during pregnancy as no information from controlled clinical studies is available on its use in pregnant women.

Use in Lactation
Acarbose and/or its metabolites are secreted into milk in rats, with milk levels reaching ten times the maternal plasma levels. No information is available on the concentrations of acarbose or its metabolites which may appear in human milk following administration of acarbose. Consequently, acarbose should not be administered to nursing mothers unless the benefit outweighs the possible risk.

Paediatric Use
Since there is insufficient data on the safety and efficacy of acarbose in children, acarbose should not be used in patients under 18 years of age.

Genotoxicity
Acarbose showed no genotoxic potential in a series of assays for gene mutations, chromosomal damage and DNA damage.

Carcinogenicity
Acarbose increased the incidences of hypernephroid carcinomas and cortical adenomas of the kidneys and Leydig cell tumours in the testes of Sprague-Dawley rats at dietary concentrations of approximately 23 mg/kg/day and under conditions of severe malnutrition developing from glucosidase inhibition (reduced glucose utilisation, loss of isocaloric state).

Effect on laboratory tests
Small reductions in haematocrit occurred more often in acarbose-treated patients than in placebo-treated patients but were not associated with reductions in haemoglobin. Low serum calcium and low plasma vitamin B_6 levels were associated with acarbose therapy but were thought to be either spurious or of no clinical significance.

INTERACTIONS WITH OTHER MEDICINES

General: Certain drugs tend to produce hyperglycaemia and may lead to loss of blood glucose control. These drugs include diuretics (thiazides, furosemide), corticosteroids, phenothiazines, thyroid products, oestrogens, oral contraceptives, phenytoin, nicotinic acid,

sympathomimetics and isoniazid. When such drugs are administered to a patient receiving acarbose, the patient should be closely monitored for loss of blood glucose control.

Oral antidiabetic agents: When acarbose is prescribed in addition to existing treatment with sulfonylureas, or metformin, the dosage of the sulfonylurea or metformin must be appropriately reduced, should the blood glucose levels fall in the hypoglycaemic range. In individual cases hypoglycaemia-related impairment of consciousness may occur.

Neomycin: Due to neomycin-induced malabsorption of carbohydrate, concomitant administration of neomycin may lead to an enhanced reduction of postprandial blood glucose and to an increase in the frequency and severity of gastrointestinal adverse reactions. If the symptoms are severe, a temporary dose reduction of acarbose may be warranted.

Cholestyramine: The concomitant administration of cholestyramine may enhance the effects of acarbose, particularly the reduction of postprandial insulin levels. If both acarbose and cholestyramine therapy are withdrawn simultaneously, caution should be exercised as a rebound phenomenon has been observed in non-diabetic subjects.

Digoxin: In individual cases, acarbose may affect digoxin bioavailability, which may require dose adjustment of digoxin.

Intestinal Adsorbents: On the basis of general considerations, the simultaneous use of intestinal adsorbents (e.g. charcoal), and digestive enzyme preparations (e.g. amylase, pancreatin) may reduce the effect of acarbose and should be avoided wherever possible.

Antacids: The concomitant administration of acarbose and antacids does not alter the effect of acarbose. The administration of antacid preparations is unlikely to ameliorate the gastrointestinal symptoms of acarbose and therefore should not be recommended for this purpose.

ADVERSE EFFECTS

The majority of adverse experiences reported to acarbose are gastrointestinal, such as flatulence, diarrhoea and abdominal pain, which result from the pharmacodynamic action of the drug. The majority of symptoms are of mild or moderate intensity and are dose-dependent. In studies of ≥6 months duration, the symptoms occurred early (within 1-2 months of treatment) and improved tolerability with longer duration of treatment was observed. Failure to adhere to the prescribed diabetic diet, however, can lead to an intensification of these symptoms. Rarely, these gastrointestinal events may be severe and be confused with or due to ileus (see **CONTRAINDICATIONS**). In individual cases hypersensitive skin reactions may occur e.g. erythema, exanthema and urticaria. Rarely, cases of hepatitis and/or jaundice have been reported.

The frequency of adverse drug reactions reported with acarbose based on placebo-controlled studies with acarbose sorted by CIOMS III categories of frequency (placebo-controlled studies in clinical trial database: acarbose N = 8,595; placebo N = 7,278; status: 10 Feb 2006) are summarized in the table below**.**

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10),

uncommon (≥ 1/1,000 to <1/100) and rare (≥ 1/10,000 to < 1/1,000).

System Organ Class (MedDRA)	Very Common >10%	Common ≥1% to <10%	Uncommon ≥0.1% to <1%	Rare ≥0.01% to <0.1%
Vascular Disorders				Oedema
Gastrointestinal Disorders	Flatulence	Diarrhoea Gastrointestinal and abdominal pains	Nausea Vomiting Dyspepsia	
Hepatobiliary Disorders			Hepatic enzymes increased	Jaundice

Soft stools are often produced by acarbose, but if the dosage of the individual case is too high, or after simultaneous ingestion of cane sugar, the stools can become unformed or even liquid. Should diarrhoea persist, patients should be closely monitored and the dosage reduced, or therapy withdrawn, if necessary.

In addition events reported as liver disorder, hepatic function abnormal, and liver injury have been received especially from Japan. Five cases of fulminant hepatitis with fatal outcome have been reported in Japan. A relationship to acarbose cannot be excluded.

Post Marketing Adverse Event Reports:

Blood and Lymphatic System Disorders:
Unknown frequency: Thrombocytopenia

Immune System Disorders:
Unknown frequency: Allergic reaction (rash, erythema, exanthema, urticaria)

Gastrointestinal Disorders:
Unknown frequency: Subileus/ileus, Pneumatosis cystoides intestinalis

Hepatobiliary Disorders:
Unknown frequency: Hepatitis

Elevated Serum Transaminase Levels: See **PRECAUTIONS**

DOSAGE AND ADMINISTRATION

Since the activity and the tolerability of acarbose varies from individual to individual, the optimal dosage must be individualised.

GLYBOSAY should be swallowed whole with a little liquid directly before a meal or chewed with the first few mouthfuls of the meal.

In adults, GLYBOSAY should be started at a low initial dose and be increased slowly to minimise the gastrointestinal side effects. Treatment is usually commenced at 50 mg once daily for the first week, 50 mg twice daily for the second week and 50 mg three times a day for the third week. A further increase of the dose may be necessary after 4 - 8 weeks on the basis of the blood glucose level. The average adult dose is 100 mg GLYBOSAY three times daily. A further increase to 200 mg GLYBOSAY three times daily may occasionally be necessary (see **PRECAUTIONS**).

If gastrointestinal symptoms are not tolerated despite close adherence to the prescribed diet, a reduction in the dose should be considered.

No modification of the adult dosage regimen is necessary in the elderly.

OVERDOSAGE

Overdosage of acarbose taken with food and/or drinks containing carbohydrates, can result in an exacerbation of the intestinal effects, i.e. diarrhoea, flatulence, and tympanism.

In the event of overdose with acarbose in the absence of food, excessive intestinal effects are not expected to occur. Hypoglycaemia is unlikely to occur.

Carbohydrate containing food and/or drinks should be avoided for 4-6 hours following overdosage with acarbose.

Diarrhoea should be treated by standard conservative measures.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

GLYBOSAY 50 mg are round, biconvex, white to off-white tablets, marked with “ACA 50” on one side.

GLYBOSAY 100 mg are round, biconvex, white to off-white tablets, marked with a score on one side, and “ACA 100” on the reverse side.

GLYBOSAY is available in PVC/PE/PVDC/Al blister packs of 90 tablets.

Store below 25°C. Protect from moisture.

NAME AND ADDRESS OF THE SPONSOR

Generic Partners Pty Ltd
313 Burwood Road
HAWTHORN VIC 3122
Australia

POISON SCHEDULE OF THE MEDICINE

S4: Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

14 May 2015

DATE OF MOST RECENT AMENDMENT

14 October 2015