

## Data Sheet

# GLUCOBAY®

*Acarbose tablets 50 mg and 100 mg oblong*

## Qualitative and Quantitative Composition

Glucobay 50      1 tablet contains 50 mg acarbose  
Glucobay 100    1 tablet contains 100 mg acarbose

## Pharmaceutical Form

Glucobay 50                      Tablets  
Glucobay 100                     Tablets

**Tablets 50 mg:** White to yellow-tinged round, convex tablets of 7 mm diameter and 10 mm radius of curvature. On one side the tablet code is “G” and “50” and on the other side “Bayer cross”.

**Oblong tablets 100 mg:** White to yellow-tinged oval oblong, convex tablets of 13 mm length, 6 mm width and 5.5 mm radius of curvature. On one side the tablet code is “G”, ”score” and “100” and on the other side “score”.

## Indications

Glucobay is indicated for the additional treatment of insulin dependant and non-insulin dependant diabetes mellitus in association with diet.

## Posology and Method of Administration

*Recommended usual dose for additional therapy in association with diet in patients with diabetes mellitus*

Because efficacy and tolerability vary, the dosage must be adjusted by the doctor to suit each individual patient.

### *Dosage Regimen*

Unless otherwise prescribed the recommended dosage is as follows:

Initially	3 x 1 tablet of	50 mg Glucobay/day	or	3 x ½ tablet of	100mg Glucobay/day
Up to	3 x 2 tablets of	50 mg Glucobay/day	or	3 x 1 tablet of	100mg Glucobay/day

A further increase in dosage to 3 x 200 mg Glucobay/day may occasionally be necessary.

The dose may be increased after 4 – 8 weeks. An increase can also be made later in the course of the treatment if the patient shows an inadequate clinical response. If side effects occur in spite of strict adherence to the diet, the dose should not be increased, and if necessary should be reduced. The average

dose is 300mg Glucobay/day (corresponding to 3 x 2 tablets of Glucobay 50 /day, or 3 x 1 tablet of Glucobay 100 /day).

***Method of Administration***

Glucobay tablets are effective only if swallowed whole with a little liquid directly before the meal or chewed with the first few mouthfuls of the meal.

***Special Monitoring Advice***

(see Special Warnings and Precautions for Use)

***Geriatric patients***

No alteration of dosage or dosing frequency is necessary for elderly patients.

***Children and adolescents***

(see Special Warnings and Precautions for Use)

***Patients with Hepatic impairment***

No dose adjustment is required in patients with pre-existing impaired hepatic function

***Patients with Renal impairment***

(see contraindications)

## **Contraindications**

Hypersensitivity to acarbose and/or to inactive constituents.

Chronic intestinal disorders associated with distinct disturbances of digestion and absorption.

States which may deteriorate as a result of increased gas formation in the intestine (e.g. Roemheld's syndrome, major hernias, intestinal obstructions, and intestinal ulcers).

Glucobay tablets are contraindicated in patients with severe renal impairment (creatinine clearance < 25 mL/min).

## **Special Warnings and Precautions for Use**

Asymptomatic liver enzyme elevations may occur in individual cases. Therefore liver enzyme monitoring should be considered during the first 6 to 12 months of treatment. In evaluable cases these changes were reversible on discontinuation of Glucobay therapy.

Safety and efficacy of Glucobay in patients under 18 years of age have not been established.

## **Interaction with Other Medicaments and Other Forms of Interaction**

Sucrose (cane sugar) and foods containing sucrose often cause abdominal discomfort or even diarrhoea during treatment with Glucobay as a result of increased carbohydrate fermentation in the colon.

Glucobay has an antihyperglycaemic effect, but does not itself induce hypoglycaemia. If Glucobay is prescribed in addition to sulphonylurea, metformin or insulin, a fall of the blood glucose into the hypoglycaemic range may necessitate a decrease in the sulphonylurea, metformin or insulin dose. In individual cases hypoglycaemic shock may occur.

If acute hypoglycaemia develops it should be borne in mind that sucrose (cane sugar) is broken down into fructose and glucose more slowly during treatment with Glucobay; for this reason sucrose is unsuitable for a rapid alleviation of hypoglycaemia and glucose should be used instead.

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

Because they may possibly influence the action of Glucobay simultaneous administration of cholestyramine, intestinal absorbents and digestive enzyme products should be avoided. No interaction was observed with dimeticone/simeticone.

The concomitant administration of Glucobay and oral neomycin may lead to enhanced reductions of postprandial blood glucose and to an increase in the frequency and severity of gastrointestinal side-effects. If the symptoms are severe, a temporary dose reduction of Glucobay may be considered.

## Pregnancy and Lactation

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

After administration of radiolabelled acarbose to lactating rats a small quantity of the radioactivity was found in the milk. There are as yet no corresponding findings in humans. However, as drug-induced effects of acarbose in milk have not been excluded in babies, in principle it is advisable not to prescribe Glucobay during the breastfeeding period.

## Effects on ability to drive or use machines

No data on impaired ability to drive and operate machinery are available for Glucobay.

## Undesirable Effects

The frequencies of Adverse Drug Reactions (ADRs) reported with Glucobay based on placebo-controlled studies with Glucobay 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 ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ) and rare ( $\geq 1/10,000$  to  $< 1/1,000$ ).

The ADRs identified only during postmarketing surveillance (status: 31 Dec 2005), and for which a frequency could not be estimated, are listed under "unknown" in bold italics below.

System organ class (MedDRA)	Very Common >10%	Common $\geq 1\%$ to $< 10\%$	Uncommon $\geq 0.1\%$ to $< 1\%$	Rare $\geq 0.01\%$ to $< 0.1\%$	Unknown
<b>Blood and Lymphatic System Disorders</b>					
					<b><i>Thrombocytopenia</i></b>
<b>Immune System Disorders</b>					

					<b>Allergic reaction (rash, erythema, exanthema, urticaria)</b>
<b>Vascular Disorders</b>					
				Oedema	
<b>Gastrointestinal Disorders</b>					
	Flatulence	Diarrhoea  Gastrointestinal and abdominal pains	Nausea  Vomiting  Dyspepsia		<b>Subileus/ Ileus</b>  <b>Pneumatosis cystoids intestinals</b>
<b>Hepatobiliary Disorders</b>					
			increase in liver enzymes	Jaundice	<b>Hepatitis</b>

In addition 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 been reported in Japan. The relationship to Glucobay is unclear.

If the prescribed diabetic 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.

In patients receiving the recommended daily dose of 150 to 300 mg Glucobay/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 Glucobay therapy (see *Special Warnings and Precautions for Use*).

## Overdose

When Glucobay is taken with drinks and/or meals containing carbohydrates (polysaccharides, oligosaccharides, or disaccharides), overdosage can lead to meteorism, flatulence, and diarrhoea. If an overdose of Glucobay is taken without food excessive intestinal symptoms are unlikely.

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

## Pharmacodynamic Properties

The active ingredient of Glucobay tablets is acarbose, a pseudotetrasaccharide of microbial origin. Glucobay can be used for the treatment of insulin-dependent (IDDM) and non-insulin-dependent (NIDDM) diabetes.

In all species tested acarbose exerts its activity in the intestinal tract. The action of acarbose is based on inhibition of the intestinal enzymes ( $\alpha$ -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 postpones and 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.

Acarbose lowers abnormally high concentrations of glycosylated haemoglobin.

## Pharmacokinetic Properties

The pharmacokinetics of Glucobay were investigated after oral administration of the radioactively labelled substance (200mg) to healthy volunteers.

### *Absorption*

Since on average 35% of the total radioactivity (sum of the inhibitory substance and any degradation products) was excreted by the kidneys within 96 hours, it can be assumed that the degree of absorption is at least in this range.

The course of the total radioactivity concentration in plasma went through two peaks. The first peak, with an average acarbose-equivalent concentration of  $52.2 \pm 15.7$  microgram/L after  $1.1 \pm 0.3$  hours, is in agreement with corresponding data for the concentration course of the inhibitor substance ( $49.5 \pm 26.9$  microgram/L after  $2.1 \pm 1.6$  hours). The second peak is on average  $586.3 \pm 282.7$  microgram/L and is reached after  $20.7 \pm 5.2$  hours. In contrast to the total radioactivity, the maximum plasma concentrations of the inhibitory substance are lower by a factor of 10 – 20. The second, higher peak after about 14-24 hours is believed to be due to absorption of bacterial degradation products from deeper parts of the intestine.

### *Distribution*

A relative volume of distribution of 0.32 L/kg bodyweight has been calculated in healthy volunteers from the concentration course in the plasma (intravenous dosing, 0.4 mg/kg b.w.)

### *Bioavailability*

The bioavailability is 1-2 % only. This extremely low systemically available percentage of inhibitory substance is desirable because acarbose acts only locally in the intestine. Thus, this low bioavailability has no relevance for the therapeutic effect.

### *Metabolism and Elimination*

The plasma elimination half-lives of the inhibitory substance are  $3.7 \pm 2.7$  hours for the distribution phase and  $9.6 \pm 4.4$  hours for the elimination phase.

The proportion of inhibitory substance excreted in the urine was 1.7% of the administered dose. 51% of the activity was eliminated within 96 hours in the faeces.

## Preclinical Safety Data

### *Acute toxicity*

Acute toxicity studies after oral and intravenous administration of acarbose have been conducted in mice, rats and dogs. The results of the acute toxicity studies are summarised in the table below.

Species	Sex	Route of Administration	LD <sub>50</sub> SIU/kg <sup>(3)</sup>	Confidence limits for p<0.05
Mouse	m <sup>(1)</sup>	per os	> 1,000,000	
Mouse	m	i.v.	> 500,000	
Rat	m	per os	> 1,000,000	
Rat	m	i.v.	478,000	(421,000 - 546,000)

Rat	f <sup>(2)</sup>	i.v.	359,000	(286,000 - 423,000)
Dog	m and f	per os	> 650,000	
Dog	m and f	i.v.	> 250,000	

(1) Male

(2) Female

(3) 65,000 SIU correspond to about 1g of the product (SIU = saccharase inhibitory units)

On the basis of these results acarbose may be described as non-toxic after single oral doses; even after doses of 10g/kg an LD<sub>50</sub> could not be determined. Moreover, no symptoms of intoxication were observed in any of the test species in the dose range under investigation.

The substance is also practically non-toxic after i.v. administration.

#### ***Subchronic toxicity***

Tolerability studies have been conducted in rats and in dogs over periods of 3 months. In rats acarbose has been investigated in doses of 50-450 mg/kg p.o. All haematological and clinicochemical parameters remained unchanged compared to a control group receiving no acarbose. Subsequent histo-pathological investigations similarly yielded no evidence of damage at any dose.

Doses of 50-450 mg/kg p.o. have also been investigated in dogs. Compared to a control group which received no acarbose, changes due to the test substance were demonstrated in the gain of body weight,  $\alpha$ -amylase activity in the serum, and the blood urea concentration. In all dose groups, when the constant quantity of 350g feed/day was given, the body weight gain mean group values fell markedly during the first 4 weeks of the study. When the quantity of feed provided had been increased to 500 g/day in the 5<sup>th</sup> week of the study, the animals remained at the same weight level. These weight changes induced by acarbose in quantities exceeding the therapeutic dose should be regarded as an expression of increased pharmacodynamic activity of the test substance due to an isocaloric feed imbalance (loss of carbohydrates); they do not represent an actual toxic effect. The slight increases in the urea concentration should also be regarded as an indirect result of the treatment, i.e. of a catabolic metabolic situation developing with the loss in weight. The diminished  $\alpha$ -amylase activity can also be interpreted as a sign of increased pharmacodynamic effect.

#### ***Chronic toxicity***

Chronic studies have been conducted in rats, dogs, and hamsters, with respective treatment durations of 24 months, 12 months, and 80 weeks. In addition to the question of damage caused by chronic administration, the studies in rats and hamsters were also intended to address possible carcinogenic effects.

#### ***Carcinogenicity***

A number of studies are available on carcinogenicity.

Sprague-Dawley rats received up to 4500 ppm acarbose in feed over a period of 24-26 months. Administration of acarbose in the feed caused considerable malnutrition in the animals. Under these study conditions, tumours of the renal parenchyma (adenoma, hypernephroid carcinoma) were found dose-dependently compared to the controls, while the overall tumour rate (in particular the rate for hormone dependent tumours) decreased.

To prevent malnutrition, in subsequent studies the animals received glucose substitution. At a dose of 4500 ppm acarbose plus glucose substitution, the body weight was 10% lower than in the control group. An increased incidence of renal tumours was not observed. When the study was repeated without glucose substitution over a 26 month period, an increase in benign tumours of Leydig cells of the testes was also observed. In all groups receiving glucose substitution the glucose values were (sometimes pathologically) elevated (alimentary diabetes on administration of large quantities of glucose).

On administration of acarbose via a stomach tube the body weights were within the control range, and with this study design elevated pharmacodynamic activity was avoided. The tumour rate was normal.

Wistar rats received 0-4500 ppm acarbose for 30 months in feed or via a stomach tube. Administration of acarbose in the feed did not lead to any pronounced weight loss. From 500 ppm acarbose the caecum was enlarged. The overall tumour rate decreased, and there was no evidence of an increased incidence of tumours.

Hamsters received 0-4000 ppm acarbose in feed over 80 weeks, with and without glucose substitution. Increased blood glucose concentrations were seen in animals of the highest dose group. Tumour incidences were not elevated.

### ***Reproduction toxicology***

Investigations for teratogenic effects were conducted in rats and in rabbits, using doses of 0, 30, 120 and 480 mg/kg p.o. in both species. In the rats the treatment was administered from the 6<sup>th</sup> to the 15<sup>th</sup> day of gestation, and in the rabbits from the 6<sup>th</sup> to the 18<sup>th</sup> day of gestation. There was no evidence of teratogenic effects due to acarbose in either species in the range of doses under test.

No impairment of fertility was observed in male or female rats up to a dose of 540 mg/kg/day.

Administration of up to 540 mg/kg/day during foetal development and lactation in rats had no effect on the birth process or the young. No data are available on the use of Glucobay during pregnancy and lactation in humans.

### ***Mutagenicity***

According to a number of mutagenicity studies, there is no evidence of any genotoxic action of acarbose.

## **Pharmaceutical Particulars**

### ***List of Excipients***

Microcrystalline cellulose; Silica, colloidal anhydrous; magnesium stearate; maize starch.

### ***Shelf-life***

Blister pack, PVC.	36 months from date of manufacture stored at or below 30°C.
Blister pack, polypropylene.	36 months from date of manufacture, stored at or below 30°C.

### ***Special Precautions for Storage***

None

### ***Nature and Contents of Container***

Glucobay 50 – packs of 90 tablets.  
Glucobay 100 – packs of 90 tablets.

### ***Instruction for Use / Handling***

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 higher relative humidity, discoloration can occur in tablets that are not in the pack. The tablets should therefore only be removed from the foil or bottle immediately prior to use.

## **Medicine Classification**

Prescription Medicine

## **Name and Address**

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