α-Glucosidase inhibitor **Tablets**

Glucobay®

Prescription use only

Name of the Medicinal Product

Glucobay 50 mg tablets
Glucobay 100 mg tablets

Qualitative And Quantitative composition:

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

Pharmaceutical Form

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”.

Tablets 100 mg : White to yellow-tinged round, convex tablets of 9 mm diameter and 15 mm radius of curvature. On one side the tablet code is “G”,”score” and “100” and on the other side the “Bayer cross”.

Indications

Additional therapy in association with diet in patients with diabetes mellitus.

Dosage And Method of Administration

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

The dosage must be adjusted by the doctor to suit each patient, because efficacy and tolerability vary from one individual to another.

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 100 mg Glucobay/day
up to 3 x 2 tablets of 50 mg Glucobay/day or 3 x 1 tablet of 100 mg 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, and if patients show an inadequate clinical response in the later course of the treatment. If distressing complaints develop in spite of strict adherence to the diet, the dose should not be increased further, and if necessary should be somewhat reduced. The average dose is 300 mg Glucobay/day (corresponding to 3 x 2 tablets of Glucobay tablets 50 mg/day, or 3 x 1 tablet Glucobay tablets 100 mg/day).

Method of administration:

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

Special monitoring advice: see Special Warnings and Precautions for Use.

Additional information on special populations

Children and adolescents: see Special Warnings and Precautions for Use.

Geriatric patients:
No alteration of dosage or dosing frequency is recommended with regard to the age of the patients.

Patients with renal impairment: see Contraindications.

Duration of use: It is not envisaged that there will be any time restriction in the use of Glucobay tablets.

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

Special Warnings And Precautions For Use

In clinical trials at doses of 50 mg t.i.d. and 100 mg t.i.d., the incidence of serum transaminase elevations with Glucobay was the same as placebo. In long-term studies (up to 12 months, and including Glucobay 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 Glucobay -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 Glucobay 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.

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

Interaction With Other Medicinal Products And Other forms of Interaction

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

fermentation in the colon.

Glucobay has an antihyperglycaemic effect, but does not itself induce hypoglycaemia.

If Glucobay tablets are prescribed in addition to drugs containing sulphonylureas or metformin, or in addition to insulin, a fall of the blood glucose values into the hypoglycaemic range may necessitate a suitable 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 tablets, simultaneous administration of cholestyramine, intestinal adsorbents and digestive enzyme products should be avoided.

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 gastro-intestinal side-effects. If the symptoms are severe, a temporary dose reduction of Glucobay may be considered.

No interaction was observed with dimeticone/simeticone.

Pregnancy And Lactation

Pregnancy

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

Lactation

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 breast-feeding period.

Effects On Ability To Drive And Use Machines

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

Undesirable Effects

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. Rarely, these gastrointestinal events may be severe and be confused with or due to ileus (see Contraindications).

The frequencies of 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: Glucobay 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).
The ADRs identified only during postmarketing surveillance (status: 31 Dec 2005), and for which a frequency could not be estimated, are listed under "not known".

System Organ Class (MedDRA)	**Very common**	**Common**	**Uncommon**	**Rare**	**Not known**
Blood and lymphatic system disorders					Thrombo-cytopenia
Immune system disorders				Allergic reaction (rash, erythema, exanthema, urticaria)	
Vascular disorders				Oedema	
Gastrointestinal disorders	Flatulence	Diarrhea Gastrointestinal and abdominal pains Distension	Nausea Vomiting Dyspepsia Anorexia Gastrointestinal disorder Tenesmus Stool discolouration Gastritis Asthenia	Subileus/Ileus	Pneumatosis cystoidis intestinalis
Hepatobiliary Disorders			increase in liver enzymes	Jaundice Hepatitis	

< The MedDRA preferred term is used to describe a certain reaction and its synonyms and related conditions. ADR term representation is based on MedDRA version 11.1. >

In controlled studies, the only significant difference between acarbose and placebo in the incidence of adverse events were gastrointestinal symptoms (eg. flatulence, diarrhea and abdominal pain) which can be minimised by starting on a low dose and titrating slowly (see Dosage And Administration).

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.

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 the blood glucose values into the hypoglycaemic range may occur.
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. Six cases of pneumatosis cystoides intestinalis (PCI) have been reported in Japan.

Elevated serum transaminase levels: See Special Warnings And Precautions For Use.

Other Abnormal Laboratory Findings: Small reductions in haematocrit occurred more often in GLUCOBAY-treated patients than in placebo-treated patients but were not associated with reductions in haemoglobin. Low serum calcium and low plasma vitamin B6 levels were associated with GLUCOBAY therapy but were thought to be either spurious or of no clinical significance.

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 tablets are taken with drinks and/or meals containing carbohydrates (disaccharides, oligosaccharides or polysaccharides), overdosage can lead to meteorism, flatulence and diarrhea.

In the event of Glucobay tablets being taken in an overdose independently of food, excessive intestinal symptoms need not be anticipated.

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

Pharmacological Properties

Pharmacodynamic Properties

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.

Pharmacokinetics Properties

Absorption: One to 2% of an oral dose of acarbose is absorbed from the gastrointestinal tract as unchanged drug. After the oral administration of 200mg ^{14}C-labelled acarbose (200mg) 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.

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.

Pharmaceutical Particulars

List of excipients:
Microcrystalline cellulose, silicia, colloidal anhydrous, magnesium stearate, maize starch

Incompatibilities: None

Shelf-life: Please refer to labels

Special precautions for storage: Do not store above 30^{o}C.

Nature and contents of container: Packs containing 10 blisters x 10 tablets

Instructions for use / handling:
The tablets should only be removed from the foil or bottle immediately prior to use.

Please read package insert carefully. Ask your doctor for more information.

Manufactured by:
Bayer AG
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