Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Glucobay 50 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Acarbose 50 mg.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Tablets.
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.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Indications
Glucobay is recommended:
1. as an adjunct to diet, in combination with insulin, in the management of insulin dependent diabetes mellitus (IDDM), or
2. as an adjunct to diet, alone or in combination with insulin or oral hypoglycaemic agents, in the management of non-insulin dependent diabetes mellitus (NIDDM).

Mode of action
Glucobay is a competitive inhibitor of intestinal alpha-glucosidases with maximum specific inhibitory activity against sucrase. Under the influence of Glucobay, the digestion of starch and sucrose into absorbable monosaccharides in the small intestine is dose-dependently delayed. In diabetic subjects, this results in a lowering of postprandial hyperglycaemia and a smoothing effect on fluctuations in the daily blood glucose profile.

In contrast to sulphonylureas Glucobay has no stimulatory action on the pancreas.

Treatment with Glucobay also results in a reduction of fasting blood glucose and to modest changes in levels of glycated haemoglobin (HbA_1, HbA_{1c}). The changes may be a reduction or reduced deterioration in HbA_1 or HbA_{1c} levels, depending upon the patient's clinical status and disease progression. These parameters are affected in a dose-dependent manner by Glucobay.

Following oral administration, only 1-2% of the active inhibitor is absorbed.

4.2 Posology and method of administration

Posology
Glucobay tablets are taken orally and should be chewed with the first mouthful of food, or swallowed whole with a little liquid directly before the meal. Owing to the great individual variation of glucosidase activity in the intestinal mucosa, there is no fixed dosage regimen, and patients should be treated according to clinical response and tolerance of intestinal side-effects.

Adults
The recommended initial dose is 50mg three times a day. However, some patients may benefit from more gradual initial dose titration to minimise gastrointestinal side-effects. This may be achieved by initiating treatment at 50mg once or twice a day, with subsequent titration to a three times a day regimen.

If after six to eight weeks of treatment patients show an inadequate clinical response, the dosage may be increased to 100mg three times a day. A further increase in dosage to a maximum of 200mg three times a day may occasionally be necessary. Patients receiving the maximum dose require careful monitoring (see Special warnings and precautions for use, Section 4.4).

Glucobay is intended for continuous long-term treatment.

Elderly
No modification of the normal adult dosage regimen is necessary.

Children
Dosage has not been established.

The safety and efficacy of Glucobay 50mg and 100mg tablets in children and adolescents under 18 years of age have not yet been established.

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.

Dosage regimen
Unless otherwise prescribed the recommended dosage is as follows.
Initially 3x 1 tablet of 50 mg Glucobay/day or
3x ½ tablet of 100 mg Glucobay/day
up to 3x 2 tablets of 50 mg Glucobay/day or
3x 1 tablet of 100 mg Glucobay/day

A further increase in dosage to 3x 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 3x 2 tablets of Glucobay tablets 50 mg/day, or 3x 1 tablet of Glucobay tablets 100 mg/day).

Recommended usual dose for the prevention of type 2 diabetes in patients with impaired glucose tolerance;

Recommended dose: 3x 100 mg/day
Treatment should be initiated with a dose of 50 mg once daily and escalated to 3x 100 mg/day within 3 months.

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.

4.3 Contraindications

Hypersensitivity to acarbose or any of the excipients, use in pregnancy and in nursing mothers. Glucobay is also contra-indicated 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, e.g. larger hernias.

As Glucobay has not been studied in patients with severe renal impairment, it should not be used in patients with a creatinine clearance < 25 ml/min/1.73m^2.

Glucobay is also contra-indicated in patients with severe hepatic impairment (e.g. liver cirrhosis)

4.4 Special warnings and precautions for use

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

Transaminases: Cases of fulminant hepatitis have been reported during Glucobay therapy. The mechanism is unknown, but Glucobay may contribute to a multifactorial pathophysiology of liver injury. If elevations of liver enzymes are observed, a reduction in dosage or withdrawal of therapy may be indicated, particularly if the elevations persist. In such circumstances, patients should be monitored at weekly intervals until normal values are established. It is recommended that liver enzyme monitoring is considered during the first 6 to 12 months of treatment (see section 4.8: Undesirable effects). No dose adjustment is required in patients with pre-existing impaired hepatic function, however, liver enzymes should be closely monitored.
Glucobay must not be used as a substitute for dietary control. It is intended primarily to minimise the postprandial serum glucose peaks that are often difficult to control.

It should be used only under diabetic specialist direction.

Glucobay has an antihyperglycaemic effect, but does not itself induce hypoglycaemia. If Glucobay is prescribed in addition to other blood glucose lowering drugs (e.g sulphonylureas metformin, or insulin) a fall of the blood glucose values into the hypoglycaemic range may require a dose adaption of the respective co-medication. If acute hypoglycaemia develops glucose should be used for rapid correction of hypoglycaemia. (see: section 4.5: Interaction with other medicinal products and other forms of interaction).

4.5 Interaction with other medicinal products and other forms of interactions

The simultaneous administration of cholestyramine, intestinal adsorbents (e.g. charcoal) and medicinal products with digestive enzymes (e.g. amylase, pancreatin) should be avoided as they may possibly influence the action of Glucobay.

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.

In isolated cases, Glucobay may affect digoxin bioavailability, leading to either a decrease or an increase in plasma levels of digoxin. Dose adjustment of digoxin may be required.

The administration of antacid preparations containing magnesium and aluminium salts, e.g. hydrotalcite, has been shown not to ameliorate the acute gastro-intestinal symptoms of Glucobay and should therefore not be recommended to patients for this purpose.

Glucobay has an anti-hyperglycaemic effect but, by itself, does not cause hypoglycaemia. In patients treated simultaneously with Glucobay and sulphonylurea, metformin or insulin, the glycaemia values may drop to hypoglycaemic levels and so dose adjustment of these medicinal products may be necessary.

Isolated reports of hypoglycaemic shock have been received. In the event of acute hypoglycaemia, it should be considered that the biotransformation of sucrose into fructose and glucose is slower during treatment; for this reason, sucrose is not suitable for fast relief from hypoglycaemia and glucose should be used instead. This is because Glucobay will delay the digestion and absorption of disaccharides, but not monosaccharides.

During treatment with Glucobay, sucrose (cane sugar) as well as foods containing sucrose, often cause abdominal discomfort or even diarrhoea as a result of the increased fermentation of carbohydrates in the colon.

4.6 Fertility, pregnancy and lactation

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

After the administration of radioactively marked acarbose to nursing rats, a small amount of radioactivity was recovered in the milk. To date there have been no similar findings in humans.

Nevertheless, as the possibility of drug induced effects on nursing infants can not be excluded, the prescription of Glucobay is not recommended during breastfeeding.

4.7 Effects on ability to drive and use machines

No data are available on alteration of the ability to drive vehicles or use machines while on treatment with Glucobay.

4.8 Undesirable effects

The undesirable effects of acarbose found in the placebo controlled clinical trials and classified according to CIOMS III frequency categories (placebo controlled studies in the clinical trial database: acarbose N = 8595; placebo N = 7278; status: 10 February 2006) are described 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					Thrombocytopenia
Immune system disorders					Drug hypersensivity and hypersensivity (rash, erythema, exanthema, urticaria)
Vascular disorders				Oedema	
Gastrointestinal disorders	Flatulence	Diarrhea Gastrointestinal and abdominal pains	Nausea Vomiting Dyspepsia		Subileus/Ileus Pneumatosis cystoidis intestinalis[1]
Hepatobiliary Disorders			increase in transami-na ses.	Jaundice	Hepatitis
Skin and subcutaneous tissue disorders					Acute generalised exanthematous pustulosis

< 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 postmarketing, cases of liver disorder, abnormal hepatic function, and liver injury have been reported. Individual cases of fulminant hepatitis with a fatal outcome have also been reported, particularly from Japan.

The lack of compliance with the prescribed diet may give rise to intensification of intestinal side effects. In the event that they should appear in spite of complying with the prescribed diabetic diet, the doctor should be consulted and the dose reduced either temporarily or permanently.

In patients treated with the recommended daily dose of 150 mg to 300 mg Glucobay a day, clinically relevant abnormal liver function tests (3 times above normal limits) were rarely observed. Abnormal values may be transient during treatment with Glucobay (see section 4.4: Special warnings and precautions for use).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

When Glucobay tablets are taken with drinks and/or meals containing carbohydrates overdose may lead to meteorism, flatulence and diarrhoea. If Glucobay tablets are taken in overdose independently of food, excessive intestinal symptoms need not be anticipated. No specific antidotes to Glucobay are known.

Intake of carbohydrate-containing meals or beverages should be avoided for 4-6 hours.

Diarrhoea should be treated by standard conservative measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

In all species tested, acarbose exerts its activity in the intestinal tract. The action of acarbose is based on the competitive inhibition of 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. Glucose derived from these carbohydrates is released and taken up into the blood more slowly. In this way, acarbose reduces the postprandial rise in blood glucose, thus reducing blood glucose fluctuations.

In a prospective, randomised, placebo-controlled, double-blind study of Glucobay treatment over 3-5 years (mean treatment duration 3.3 years), which included 1,429 subjects with confirmed impaired glucose tolerance and a body mass index between 25 and 40, treatment with Glucobay was associated with a 49% relative risk reduction in the development of cardiovascular events (p=0.03) and a 2.5% absolute reduction in the observed incidence rates (observed incidence 4.7% PLA versus 2.2% Glucobay).

Among cardiovascular events, the major reduction was in the risk of myocardial infarction, relative risk reduction 91% (p=0.02) and a 1.6% absolute reduction in the observed incidence rates (observed incidence 1.7% PLA versus 0.1% Glucobay).

Glucobay was also associated with a 34% relative risk reduction for new cases of hypertension (p=0.006) and a 5.4% absolute reduction in the observed incidence rates (observed incidence 16.8% PLA versus 11.4% Glucobay).

These cardiovascular effects were confirmed in a meta-analysis of 7 placebo-controlled trials of Glucobay in the treatment of type 2 diabetes, which included a total of 2,180 patients, of whom 1,248 were treated with Glucobay and 932 with placebo. In these patients the risk of MI was relatively reduced by 64% (p=0.01; and an estimated absolute risk reduction of 1.2% after one year of treatment, 2.0% PLA versus 0.8% Glucobay). The risk of all cardiovascular events decreased by 24% (p=0.02; and an estimated absolute risk reduction of 3.4% after one year of treatment, 15.1% PLA versus 11.7% Glucobay).

5.2 Pharmacokinetic properties

Following administration, only 1-2% of the active inhibitor is absorbed.

The pharmacokinetics of Glucobay were investigated after oral administration of the ^{14}C-labelled substance (200mg) to healthy volunteers. On average, 35% of the total radioactivity (sum of the inhibitory substance and any degradation products) was excreted by the kidneys within 96 h. The proportion of inhibitory substance excreted in the urine was 1.7% of the administered dose. 50% of the activity was eliminated within 96 hours in the faeces. The course of the total radioactivity concentration in plasma was comprised of two peaks. The first peak, with an average acarbose-equivalent concentration of 52.2 ± 15.7µg/l after 1.1 ± 0.3 h, is in agreement with corresponding data for the concentration course of the inhibitor substance (49.5 ± 26.9µg/l after 2.1 ± 1.6 h). The second peak is on average 586.3 ± 282.7µg/l and is reached after 20.7 ± 5.2 h. The second, higher peak is due to the absorption of bacterial degradation products from distal parts of the intestine. In contrast to the total radioactivity, the maximum plasma concentrations of the inhibitory substance are lower by a factor of 10-20. The plasma elimination half-lives of the inhibitory substance are 3.7 ± 2.7 h for the distribution phase and 9.6 ± 4.4 h for the elimination phase.

A relative volume of distribution of 0.32 l/kg/body-weight has been calculated in healthy volunteers from the concentration course in the plasma.

5.3 Preclinical safety data

There was no evidence of a teratogenic effect of acarbose in studies with oral doses of up to 480mg/kg/day in rats and rabbits.

In rats no impairment of fertility was observed in males or females at doses of up to 540mg/kg/day. The oral administration of up to 540mg/kg/day to rats during foetal development and lactation had no effect on parturition or on the young.

The results of a number of mutagenicity studies show no evidence of a genotoxic potential of acarbose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Colloidal anhydrous silica
Magnesium stearate
Maize starch

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25 °C. Store in the original package.

6.5 Nature and contents of container

Blister strips comprising 300µm polypropylene foil (colourless) with a 20µm soft aluminium backing foil, in cardboard outers.

Pack size: 90

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Bayer Limited
The Atrium
Blackthorn Road
Dublin 18
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8 MARKETING AUTHORISATION NUMBER

PA1410/029/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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