

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Acarbose 50 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg acarbose.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
A white to off-white, 9/32" round, biconvex tablet debossed with A over 50 on one side of the tablet and M on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Acarbose is indicated in adults and adolescents aged over 18 years.
Acarbose is recommended for the treatment of type II diabetes mellitus in patients inadequately controlled on diet alone, or on diet and oral hypoglycaemic agents.

4.2 Posology and method of administration

Posology

Adults

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.

The recommended initial dose is 50 mg 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 50 mg once or twice a day, with subsequent titration to a three times a day regimen.

If after six to eight weeks' treatment patients show an inadequate clinical response, the dosage may be increased to 100 mg three times a day. A further increase in dosage to a maximum of 200 mg three times a day may occasionally be necessary. Patients receiving the maximum dose require careful monitoring.

If distressing complaints develop in spite of strict adherence to the diet, the dose should not be increased further, and if necessary should be reduced according to the severity of the side-effects and the clinical judgement of the prescriber.

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

Acarbose is intended for continuous long-term treatment.

Elderly patients

No modification of the normal adult dosage regimen is necessary.

Patients with hepatic impairment

No dose adjustment is required in patients with pre-existing impaired hepatic function, however, liver enzymes should be closely monitored (see section 4.4).

Paediatric population

The safety and efficacy of acarbose in children and adolescents under 18 years of age have not yet been established. Acarbose is not recommended for patients under the age of 18 years.

Method of administration

Acarbose 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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Inflammatory bowel disease, colonic ulceration, partial intestinal obstruction or predisposition to intestinal obstruction. In addition, acarbose 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.
- Severe kidney impairment (creatinine clearance $<25 \text{ ml/min/1.73m}^2$) as acarbose has not been studied in patients with severe renal impairment.
- Severe hepatic impairment (e.g. liver cirrhosis).
- Pregnancy and in nursing mothers.

4.4 Special warnings and precautions for useHypoglycaemia

Acarbose has an antihyperglycaemic effect, but does not itself induce hypoglycaemia. If acarbose is prescribed in addition to other blood glucose lowering drugs (e.g. sulfonylureas, 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).

Episodes of hypoglycaemia occurring during therapy must, where appropriate, be treated by the administration of glucose, not sucrose. This is because acarbose will delay the digestion and absorption of disaccharides, but not monosaccharides.

Transaminases

Cases of fulminant hepatitis have been reported during acarbose therapy. The mechanism is unknown, but acarbose may contribute to a multifactorial pathophysiology of liver injury. Patients treated with acarbose may, on rare occasions, experience an idiosyncratic response with either symptomatic or asymptomatic hepatic dysfunction. In the majority of cases this dysfunction is reversible on discontinuation of acarbose therapy. It is recommended that liver enzyme monitoring is considered during the first six to twelve months of treatment (see section 4.8). 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.

Paediatric population

The safety and efficacy of acarbose has not been established in patients under 18 years of age.

4.5 Interaction with other medicinal products and other forms of interaction

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

may occur (i.e. clinical sequelae of glucose levels < 1 mmol/L such as altered conscious levels, confusion or convulsions).

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.

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

Intestinal adsorbents (e.g. charcoal) and digestive enzyme preparations containing carbohydrate splitting enzymes (e.g. amylase, pancreatin) may reduce the effect of acarbose and should not therefore be taken concomitantly.

The concomitant administration of acarbose 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 acarbose may be considered.

The concomitant administration of colestyramine may enhance the effects of acarbose, particularly with respect to reducing postprandial insulin levels. Simultaneous administration of acarbose and colestyramine should, therefore, be avoided. In the rare circumstance that both acarbose and colestyramine therapy are withdrawn simultaneously, care is needed as a rebound phenomenon has been observed with respect to insulin levels in non-diabetic subjects.

In isolated cases acarbose may affect the bioavailability of digoxin, making dose adjustment necessary. Monitoring of serum digoxin levels should be considered.

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

In a pilot study to investigate a possible interaction between acarbose and nifedipine, no significant or reproducible changes were observed in the plasma nifedipine profiles.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breastfeeding

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 acarbose is not recommended during breast-feeding.

Fertility

No impairment of fertility was observed in male or female rats at doses of up to 540 mg/kg/day (see section 5.3).

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 acarbose.

4.8 Undesirable effects

The frequencies of adverse drug reactions (ADRs) reported with acarbose, based on placebo-controlled studies (acarbose N = 8,595; placebo N = 7,278), are summarised 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) Rare (≥ 1/10,000 to < 1/1,000), and Not known (cannot be estimated from the available data).

The ADRs identified only during postmarketing surveillance 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 hypersensitivity and hypersensitivity (rash, erythema, exanthema, urticaria)
Vascular disorders				Oedema	
Gastrointestinal disorders	Flatulence	Diarrhoea Gastrointestinal and abdominal pains	Nausea Vomiting Dyspepsia		Subileus/Ileus Pneumatosis cystoides intestinalis
Hepatobiliary disorders			Increase in transaminases	Jaundice	Hepatitis
Skin and subcutaneous tissue disorders					Acute generalised exanthematous pustulosis

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 been reported, particularly in Japan.

In patients treated with the recommended daily dose of 150 mg to 300 mg acarbose a day, clinically relevant abnormal liver function tests (three times above upper limit of normal range) were rarely observed. Abnormal values may be transient during treatment with acarbose (see section 4.4).

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.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly 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. By reporting side effects you can help provide more information on the safety of this medicine.

4.9 Overdose

Symptoms

When acarbose is taken with beverages and/or meals containing carbohydrates (polysaccharides, oligosaccharides or disaccharides), overdose may lead to meteorism, flatulence and diarrhoea. However, in the event that acarbose has been ingested in overdose outside meal times, no excessive intestinal symptoms should be expected.

Management

In the event of overdose the intake of beverages or meals containing carbohydrates should be avoided over the next 4-6 hours.

No specific antidotes to acarbose are known.

Diarrhoea should be treated by standard conservative measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Alpha glucosidase inhibitors, ATC code: A10BF01.

Mechanism of action

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.

Under the influence of acarbose, 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. Treatment with acarbose also results in a reduction of fasting blood glucose and to modest changes in levels of glycated haemoglobin (HbA^1 , $\text{HbA}^{1\text{C}}$).

5.2 Pharmacokinetic properties

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

The pharmacokinetics of acarbose were investigated after oral administration of the ^{14}C -labelled substance (200 mg) 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 $52.2 \pm 15.7 \mu\text{g/l}$ after $1.1 \pm 0.3 \text{ h}$, is in agreement with corresponding data for the concentration course of the inhibitor substance ($49.5 \pm 26.9 \mu\text{g/l}$ after $2.1 \pm 1.6 \text{ h}$). The second peak is on average $586.3 \pm 282.7 \mu\text{g/l}$ and is reached after $20.7 \pm 5.2 \text{ h}$. 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 $3.7 \pm 2.7 \text{ h}$ for the distribution phase and $9.6 \pm 4.4 \text{ h}$ 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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

Acute toxicity

LD50 studies were performed in mice, rats and dogs. Oral LD50 values were estimated to be > 10 g/kg body-weight. Intravenous LD50 values ranged from 3.8 g/kg (dog) to 7.7 g/kg (mouse).

Sub-chronic toxicity

Three month studies have been conducted in rats and dogs in which acarbose was administered orally by gavage.

In rats, daily doses of up to 450 mg/kg body-weight were tolerated without drug-related toxicity.

In the dog study, daily doses of 50-450 mg/kg were associated with decreases in body-weight. This occurred because dosing of the animals took place shortly before the feed was administered, resulting in the presence of acarbose in the gastro-intestinal tract at the time of feeding. The pharmacodynamic action of acarbose led to a reduced availability of carbohydrate from the feed, and hence to weight loss in the animals. A greater time interval between dosing and feeding in the rat study resulted in most of the drug being eliminated prior to feed intake, and hence no effect on body-weight development was observed.

Owing to a shift in the intestinal α -amylase synthesis feedback mechanism a reduction in serum α -amylase activity was also observed in the dog study. Increases in blood urea concentrations in acarbose-treated dogs also occurred, probably as a result of increased catabolic metabolism associated with the weight loss.

Chronic toxicity

In rats treated for one year with up to 4500 ppm acarbose in their feed, no drug-related toxicity was observed. In dogs, also treated for one year with daily doses of up to 400 mg/kg by gavage, a pronounced reduction in body-weight development was observed, as seen in the sub-chronic study. Again this effect was due to an excessive pharmacodynamic activity of acarbose and was reversed by increasing the quantity of feed.

Carcinogenicity

In a study in which Sprague-Dawley rats received up to 4500ppm acarbose in their feed for 24-26 months, malnutrition was observed in animals receiving the drug substance. A dose-dependent increase in tumours of the renal parenchyma (adenoma, hypernephroid carcinoma) was also observed against a background of a decrease in the overall tumour rate. When this study was repeated, an increase in benign tumours of testicular Leydig cells was also observed. Owing to the malnutrition and excessive decrease in bodyweight gain these studies were considered inadequate to assess the carcinogenic potential of acarbose.

In further studies with Sprague-Dawley rats in which the malnutrition and glucose deprivation were avoided by either dietary glucose supplementation or administration of acarbose by gavage, no drug-related increases in the incidences of renal or Leydig cell tumours were observed.

In an additional study using Wistar rats and doses of up to 4500ppm acarbose in the feed, neither drug-induced malnutrition nor changes in the tumour profile occurred. Tumour incidences were also unaffected in hamsters receiving up to 4000ppm acarbose in the feed for 80 weeks (with and without dietary glucose supplementation).

Reproductive toxicity

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 540 mg/kg/day. The oral administration of up to 540 mg/kg/day to rats during foetal development and lactation had no effect on parturition or on

the offspring.

Mutagenicity

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

Silica, colloidal anhydrous
Maize starch
Magnesium stearate
Cellulose, microcrystalline

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Clear Aclar – PVC / Aluminium blisters in cardboard carton containing 90 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Ltd t/a Gerard Laboratories
35/36 Baldoyle Industrial Estate
Grange Road
Dublin 13
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0577/171/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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