



ACCARB

1. Product name

Accarb, 50 mg and 100 mg, tablets.

2. Qualitative and Quantitative Composition

Each Accarb 50 mg tablet contains 50 mg acarbose.

Each Accarb 100 mg tablet contains 100 mg acarbose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Accarb 50 mg tablets: White to off-white round tablet, embossed with 'AA' breakline '50' on one side and 'G' on the reverse, approximately 7 mm in diameter.

Accarb 100 mg tablets: White to off-white oval shaped tablet, embossed with 'AA' breakline '100' on one side and 'G' scoreline on the reverse, approximately 13 mm x 6.5 mm.

The tablets can be divided into equal doses.

4. Clinical Particulars

4.1 *Therapeutic indications*

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

4.2 *Dose and method of administration*

Dose

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 acarbose/day or 3 x ½ tablet of 100 mg acarbose/day

Up to: 3 x 2 tablets of 50 mg acarbose/day or 3 x 1 tablet of 100 mg acarbose/day

A further increase in dosage to 3 x 200 mg acarbose/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 300 mg acarbose/day (corresponding to 3 x 2 tablets of Accarb 50 /day, or 3 x 1 tablet of Accarb 100 /day).

Special monitoring advice

(see section 4.4)

Special populations

Elderly

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

Renal impairment

(see section 4.3)

Hepatic impairment

No dose adjustment is required in patients with pre-existing impaired hepatic function (see section 4.3 and section 4.4).

Paediatric

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

Method of administration

Acarbose 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.

4.3 Contraindications

Hypersensitivity to acarbose or to any of the excipients listed in section 6.1., pregnancy and in lactating mothers.

Accarb is also contraindicated in patients with inflammatory bowel disease, colonic ulceration, partial intestinal obstruction or in patients predisposed to intestinal obstruction. In addition, Accarb should not be used in patients who have chronic intestinal diseases associated with marked disorders of digestion and 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.

Accarb is contraindicated in patients with severe hepatic impairment.

As acarbose has not been studied in patients with severe renal impairment, it should not be used in patients with a creatinine clearance < 25 mL/min/1.73m².

4.4 Special warnings and precautions for use

Hypoglycaemia: Acarbose has an antihyperglycaemic effect, but does not itself induce hypoglycaemia. If acarbose is prescribed in addition to other blood glucose lowering medicines (e.g. sulphonylureas, metformin or insulin) a fall of the blood glucose values into the hypoglycaemic range may require a dose adaptation 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. It is recommended that liver enzyme monitoring is considered during the first 6 to 12 months of treatment (see section 4.8). If elevated liver enzymes 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.

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 in higher dosage and should, therefore, not be recommended to patients for this purpose.

4.5 Interaction with other medicines and other forms of interaction

When administered alone, acarbose does not cause hypoglycaemia. It may, however, act to potentiate the hypoglycaemic effects of insulin, metformin and sulphonylurea drugs, and the dosages of these agents may need to be modified accordingly. 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).

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.

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 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 acarbose may be warranted.

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 individual cases acarbose may affect digoxin bioavailability, which may require dose adjustment of digoxin. Monitoring of serum digoxin levels should be considered.

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

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

Breast-feeding

After 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 Accarb is not recommended during breastfeeding.

Fertility

No data available. For pre-clinical fertility data refer to section 5.3.

4.7 Effects on ability to drive and use machines

Not relevant.

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 ($\geq 1/10$), 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 during post-marketing surveillance only 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, hepatic function abnormal, and liver injury have been

reported. Individual cases of fulminant hepatitis with fatal outcome have also been reported, particularly from Japan.

In patients receiving the recommended daily dose of 150 to 300 mg acarbose, clinically relevant abnormal liver function tests (three times above upper limit of normal range) were rarely observed. Abnormal values may be transient under ongoing acarbose therapy (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 suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting>.

4.9 Overdose

When acarbose tablets are taken with drinks and/or meals containing carbohydrates, overdose may lead to meteorism, flatulence and diarrhoea. If acarbose tablets are taken independently of food, excessive intestinal symptoms need not be anticipated.

No specific antidotes to acarbose are known.

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

Diarrhoea should be treated by standard conservative measures.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: drugs used in diabetes, alpha-glucosidase inhibitors

ATC code: A10BF01

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.

Mechanism of action

Acarbose is a competitive inhibitor of intestinal alpha-glucosidases with maximum specific inhibitory activity against sucrase. 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.

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

Treatment with acarbose also results in a reduction of fasting blood glucose and to modest changes in levels of glycated haemoglobin (HbA_{1c}, HbA_{1c}). The changes may be a reduction or reduced

deterioration in HbA_{1c} or HbA_{1c} levels, depending upon the patient's clinical status and disease progression. These parameters are affected in a dose-dependent manner by acarbose.

5.2 Pharmacokinetic Properties

The pharmacokinetics of acarbose were investigated after oral administration of the ¹⁴C-labelled substance (200 mg) to healthy volunteers.

Absorption

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

On average, 35% of the total radioactivity (sum of the inhibitory substance and any degradation products) was excreted by the kidneys within 96 hours. 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 ± 15.7 microgram/L after 1.1 ± 0.3 hours, is in agreement with corresponding data for the concentration course of the inhibitor substance (49.5 ± 26.9 microgram/L after 2.1 ± 1.6 hours). The second peak is on average 586.3 ± 282.7 microgram/L and is reached after 20.7 ± 5.2 hours. 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.

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.).

Elimination

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

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.

5.3 Preclinical Safety Data

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 bodyweight were tolerated without drug-related toxicity.

In the dog study, daily doses of 50 - 450 mg/kg were associated with decrease in bodyweight. 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 bodyweight 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 bodyweight 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 Studies

In a study in which Sprague-Dawley rats received up to 4500 ppm 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 4500 ppm 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 4000 ppm 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 480 mg/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 young.

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*

Accarb tablets also contain

- Microcrystalline Cellulose (PH102)
- Dried Maize Starch
- Colloidal Anhydrous Silica
- Magnesium Stearate

Accarb tablets are gluten-free, lactose-free and sugar-free.

6.2 *Incompatibilities*

Not applicable.

6.3 Shelf life

2 years.

6.4 Special Precautions for Storage

Store at or below 25°C.

6.5 Nature and contents of container

OPA/Al/PVC blister strips. Pack-sizes of 30, 90, 120 or 180 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicine Schedule

Prescription Medicine

8. Sponsor Details

Mylan New Zealand Ltd
PO Box 11-183
Ellerslie
AUCKLAND
Telephone: 09-579-2792

9. Date of First Approval

23 July 2009

10. Date of Revision of the Text

26 February 2019

Summary table of changes

Section	Summary of new information
-	Revise to SPC format
-	Minor editorial changes
3	Amendments to the descriptions of pharmaceutical form