NEW ZEALAND DATA SHEET

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/1.73m^2.

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 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. 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 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 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, intestinal absorbents and digestive enzyme products should 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. No interaction was observed with dimeticone/simeticone.

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 (≥ 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 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					Thrombo-cytopenia
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. The relationship to acarbose is unclear.

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 (polysaccharides, oligosaccharides or disaccharides), 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_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 acarbose.

5.2 Pharmacokinetic Properties

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

Absorption

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 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.

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.

5.3 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_{50} SIU/kg[3]	Confidence limits for p<0.05
Mouse	m[1]	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[2]	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_{50} 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.

Sub-chronic 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 clinic chemical parameters remained unchanged compared to acontrol 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, α-amylase activity in the serum and the blood urea concentration. In all dose groups, when the constant quantity of 350 g 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 5th 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 α-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 4,500 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 4,500 ppm acarbose plus glucose substitution, the bodyweight 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 ofthe 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 thecontrol range and with this study design, elevated pharmacodynamic activity was avoided. The tumour rate was normal.

Wistar rats received 0-4,500 ppm acarbose for 30 months in feed or via a stomach tube. Administration of acarbose in the feed did not lead to any pronounced weightloss. 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 0-4,000 ppm acarbose in feed over 80 weeks, with and without glucose substitution. Increased blood glucose concentrations were seen in animalsof the highest dose group. Tumour incidences were not elevated.

Reproductive Toxicity

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 6th to the 15th day of gestation and in the rabbits, from the 6th to the 18th 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 540mg/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 theuse of acarbose during pregnancy and lactation in humans.

Genotoxicity

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

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

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9. Date of First Approval

23 July 2009

10. Date of Revision of the Text

10 March 2022

Summary table of changes

Section	Summary of new information
4.5	Additional interaction with intestinal absorbents and digestive enzyme.
4.8	Minor editorial changes.
4.9	Minor editorial changes.
5.2	Additional information on bioavailability.
5.3	Information re-edited to fully align with brand leader.
6.1	Removed gluten, lactose and sugar free statement.
8	Sponsor details