Acarbocin

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

Dosage and Administration

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. Acarbocin is intended for continuous long-term treatment.

Dosage Regimen

Unless otherwise prescribed the recommended dosage is as follows:

Initially 1 tablet of 50 mg Acarbocin three times daily

Up to 2 tablets of 50 mg Acarbocin three times daily or 1 tablet of 100 mg Acarbocin three times daily.

A further increase in dosage to 200 mg Acarbocin three times daily 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.

**Method of Administration**

Acarbocin 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.

**Special Monitoring Advice**

See Warnings and Precautions.

**Geriatric patients**

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

**Children and adolescents**

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

**Patients with Hepatic impairment**

No dose adjustment is required in patients with pre-existing impaired hepatic function (see Contraindications, Warnings and Precautions).

**Patients with Renal impairment**

See Contraindications.

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**Contraindications**

- Hypersensitivity to acarbose and/or to any of the inactive constituents in Acarbocin
- Chronic intestinal disorders associated with distinct disturbances of digestion and absorption (e.g. Inflammatory bowel disease, colonic ulceration, partial intestinal obstruction or in patients predisposed to intestinal obstruction)
- States which may deteriorate as a result of increased gas formation in the intestine (e.g. Roemheld’s syndrome, major hernias and intestinal ulcers)
- Patients with severe renal impairment (creatinine clearance < 25 mL/min)
- Patients with hepatic impairment.
Warnings and Precautions

Hypoglycaemia
When administered alone, Acarbocin does not cause hypoglycaemia. It may, however, act to potentiate the hypoglycaemic effects of insulin 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.

Transaminases
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 6 to 12 months of treatment. If elevated transaminases are observed, withdrawal of therapy may be warranted, particularly if the elevations persist. In evaluable cases these changes were reversible on discontinuation of acarbose therapy. 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 not been shown to ameliorate the acute gastrointestinal symptoms of Acarbocin in higher dosage and should, therefore, not be recommended to patients for this purpose.

If ileus or sub-ileus is suspected, treatment must be stopped immediately (see Adverse Effects).

It is essential to adhere to a strict diabetic diet when taking Acarbocin.

Regular use of Acarbocin should not be interrupted without medical advice as this may lead to a rise in blood glucose.

Use in Pregnancy
The safety of acarbose for use in human pregnancy has not been established. An evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to reproduction, development of the embryo or foetus, the course of gestation, and peri- and postnatal development.

Acarbose is not recommended during pregnancy.

When the patient plans to become pregnant and during pregnancy, diabetes should be treated with insulin to maintain blood glucose levels as close to normal as possible in order to lower the risk of foetal malformations associated with abnormal blood glucose levels.
Use in Lactation

After administration of radio-labeled 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 Acarbocon during the breastfeeding period.

Effects on ability to drive or use machines

Acarbose monotherapy does not cause hypoglycaemia and is therefore unlikely to have effects on the ability to drive or to use machines. However, patients should be alerted to the risk of hypoglycaemia when acarbose is used in combination with metformin and/or a sulphonylurea.

Adverse Effects

The frequencies of Adverse Drug Reactions (ADRs) reported with acarbose based on placebo-controlled studies with acarbose sorted by CIOMS III categories of frequency (placebo-controlled studies in clinical database: acarbose n = 8,595; placebo n = 7,278; status: 10 Feb 2006) 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 only during postmarketing surveillance (status: 31 Dec 2005), and for which a frequency could not be estimated, are listed under “Unknown” in italics below.

<table>
<thead>
<tr>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10%</td>
<td>≥1% to &lt;10%</td>
<td>≥0.1% to &lt;1%</td>
<td>≥0.01% to &lt;0.1%</td>
<td></td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td></td>
<td></td>
<td></td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Immune System Disorders</td>
<td></td>
<td></td>
<td></td>
<td>Allergic reaction (rash, erythema, exanthema, urticaria)</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
<td>Oedema</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td>Subileus/ Ileus</td>
</tr>
<tr>
<td>Flatulence</td>
<td>Diarrhoea</td>
<td>Nausea</td>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal and abdominal pains</td>
<td>Dyspepsia</td>
<td></td>
<td>Pneumatosis cystoids intestinalis</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary Disorders</td>
<td></td>
<td></td>
<td></td>
<td>Jaundice</td>
</tr>
<tr>
<td></td>
<td>Transient increase in liver enzymes</td>
<td></td>
<td></td>
<td>Hepatitis</td>
</tr>
</tbody>
</table>

If ileus or subileus is suspected, treatment must be stopped immediately.
In addition events reported as liver disorder, hepatic function abnormal, and liver injury have been received especially from Japan. Individual cases of fulminant hepatitis with fatal outcome have been reported in Japan. The relationship to acarbose is unclear.

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 acarbose/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 acarbose therapy (see Warnings and Precautions).

### Interactions

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 Acarbocin and should not therefore be taken concomitantly. No interaction was observed with dimethicone/simethicone.

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 gastrointestinal side-effects. If the symptoms are severe, a temporary dose reduction of Acarbocin may be considered.

The concomitant administration of cholestyramine may enhance the effects of acarbose particularly with respect to reducing postprandial insulin levels. Therefore simultaneous administration of acarbose and cholestyramine should be avoided. In the rare circumstance that both acarbose and cholestyramine 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.

Several therapeutic agents including thiazide and other diuretics, corticosteroids, phenothiazines, thyroid hormones, oestrogens and oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers and isoniazid can cause hyperglycaemia, which may attenuate the pharmacodynamic effects of acarbose. Blood glucose levels should be closely monitored if any of these agents are used by patients on acarbose, or if treatment with acarbose is contemplated in patients already receiving any of these agents.

Acarbose has an antihyperglycaemic effect, but does not itself induce hypoglycaemia. If acarbose is prescribed in addition to other oral hypoglycaemic agents (e.g. a sulphonylurea, metformin or insulin), a fall of the blood glucose into the hypoglycemic range may necessitate a
Acarbocin

decrease in the sulphonylurea, metformin or insulin dose. In individual cases hypoglycemic 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 acarbose; for this reason sucrose is unsuitable for a rapid alleviation of hypoglycaemia and glucose should be used instead.

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.

**Overdose**

When Acarbocin is taken with drinks and/or meals containing carbohydrates (polysaccharides, oligosaccharides, or disaccharides), overdosage can lead to meteorism, flatulence, and diarrhoea. If an overdose of Acarbocin is taken without food excessive intestinal symptoms are unlikely.

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

No specific antidotes to Acarbocin are known.

Diarrhoea should be treated by standard conservative measures.

**Further Information**

The active ingredient of Acarbocin tablets is acarbose, a pseudotetrasaccharide of microbial origin. Acarbocin can be used for the treatment of insulin-dependent (IDDM) and non-insulin-dependent (NIDDM) diabetes.

**Actions**

Pharmacotherapeutic group: 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 inhibition of the 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. Most importantly, glucose derived from carbohydrates is released and taken up into the blood more slowly. In this way acarbose postpones and reduces the postprandial rise in blood glucose. As a result of the balancing effect on the uptake of glucose from the intestine, the blood glucose fluctuations over the day are reduced and the mean blood glucose values decrease. 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 (HbA1, HbA1c). The changes may be a reduction or
reduced deterioration in HbA1 or HbA1c levels, depending upon the patient's clinical status and disease progression. These parameters are affected in a dose-dependent manner by acarbose.

**Pharmacokinetics**

The pharmacokinetics of acarbose was investigated after oral administration of the radioactively labeled substance (200 mg) to healthy volunteers.

**Absorption**

Since 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 went through 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. In contrast to the total radioactivity, the maximum plasma concentrations of the inhibitory substance are lower by a factor of 10 – 20. The second, higher peak after about 14-24 hours is believed to be due to absorption of bacterial degradation products from deeper parts of the intestine.

**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).

**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.

**Metabolism and 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. 51% of the activity was eliminated within 96 hours in the faeces.

**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, toxicity to reproduction.

A markedly reduced body weight gain in rats and dogs after repeated administration of acarbose was considered as pharmacodynamic effect (loss of carbohydrates) and could be counteracted by increase of food or glucose supplementation.

Carcinogenicity was studied in Sprague-Dawley rats, Wistar rats and hamsters. An increased tumour incidence in certain tissues (kidney, testis) was observed if malnutrition due to acarbose was not corrected. No increase in tumour rate was observed if the body weight gain was kept normal by food or glucose supplementation.
**Acarbocin**

*Other*

Acarbose is d-Glucose, O-4,6-dideoxy-4-[[1S-(1α,4α,5β,6α)]-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl]amino]-α-d-glucopyranosyl-(1(R)4)-O-α-d-glucopyranosyl-(1(R)4)-.

Its molecular weight is 645.60 and its empirical formula is \( C_{25}H_{43}NO_{18} \).

**Excipients:**
- Cellulose - microcrystalline
- Silica - colloidal anhydrous
- Magnesium stearate
- Starch - pregelatinised maize.

**Pharmaceutical Precautions**

**Shelf life**
3 years

**Special Precautions for Storage**
Store below 25°C
Store in the original packaging to protect from moisture.

**Packaging Quantities**

<table>
<thead>
<tr>
<th>Acarbocin 50 mg tablets</th>
<th>90 tablets in PVC/PE/PVDC aluminium blister</th>
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</thead>
<tbody>
<tr>
<td>Acarbocin 100 mg tablets</td>
<td>90 tablets in PVC/PE/PVDC aluminium blister</td>
</tr>
</tbody>
</table>

**Medicine Schedule**

Prescription Medicine
Acarbocin

Sponsor Details

Boucher & Muir (New Zealand) Ltd, trading as BNM Group
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Browns Bay
Auckland 0753

Ph: 0800 565 633

Date of Preparation:

29 August 2013