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 post-prandial 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.
Acarbose lowers abnormally high concentrations of glycosylated haemoglobin.
In a prospective, randomized, placebo-controlled, double-blind study (treatment 3-5 years, average 3,3 years) with 1.429 subjects with confirmed impaired glucose tolerance* the relative risk of developing type 2 diabetes was reduced by 25%. In these patients the incidence of all cardiovascular events decreased significantly by 49%, while the incidence of MI was significantly reduced by 91%.
These effects were confirmed by a meta-analysis of 7 placebo controlled trials (total of 2180 patients, 1248 Acarbose, 932 placebos) of Acarbose in the treatment of type 2 diabetes. In these patients the risk of any cardiovascular event was reduced by 24%, while the risk of myocardial infarction was decreased by 64%. Both changes were statistically significant.

*defined as 2 hour post-glucose load plasma concentrations (2HPG) between 7.8 and 11.1 mmol/l (140-200 mg/dl) and fasting values between 5.6 and 7.0 mmol/l (100-125 mg/dl)

PHARMACOKINETIC PROPERTIES

The pharmacokinetics of acarbose was investigated after oral administration of the labelled 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 µg/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 µg/L after 2.1 ± 1.6 hours). The second peak is on average 586.3 ± 282.7 µg/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 body weight has been calculated in healthy volunteers from the concentration course in the plasma (intravenous dosing, 0.4 mg/kg b.w.).
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.
Excretion: 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

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 summarized 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	>	1000000	
Mouse	m	i.v.	>	500000	
Rat	m	per os	>	1000000	
Rat	m	i.v.		478000	(421000-546000)
Rat	f[2]	i.v.		359000	(286000-423000)
Dog	m and f	per os	>	650000	
Dog	m and f	i.v.	>	250000	

(1) Male
(2) Female
(3) 65000 SIU correspond to about 1 g 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 10 g/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.

Subchronic 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 clinicochemical parameters remained unchanged compared to a control 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 development of the animals' body weight, α-amylase activity in the serum, and the blood urea concentration. In all dose groups the body weight development was influenced in that when constant quantity of 350 g feed/day had been given the mean group values fell distinctly 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 treatment durations of respectively 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 4500 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 4500 ppm acarbose plus glucose substitution, the body weight 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 of the 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 the control range, and with this study design elevated pharmacodynamic activity was avoided. The tumour rate was normal.
Wistar rats received 0-4500 ppm acarbose for 30 months in feed or via a stomach tube. Administration of acarbose in the feed did not lead to any pronounced weight loss. 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 0-4000 ppm acarbose in feed over 80 weeks, with and without glucose substitution. Increased blood glucose concentrations were seen in animals of the highest-dose group. Tumour incidences were not elevated

Reproduction toxicology:

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 540 mg/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 the use of acarbose during pregnancy and lactation in humans.

Mutagenicity:

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

PHARMACEUTICAL PARTICULARS

List of excipients:

Microcrystalline cellulose, highly dispersed silicon dioxide, magnesium stearate, maize starch.

Special precautions for storage:

Do not store above 30°C. Keep drugs out of reach of children.

Instructions for use / handling:

At storage conditions up to 25°C and below 60 % relative humidity the unpacked tablets can be stored for up to two weeks. At higher temperatures and/or higher relative humidity, discoloration can occur in tablets that are not in the pack. The tablets should therefore only be removed from the foil or bottle immediately prior to use.

Presentation

6 -1000's per bottle or box.