ACARBOSE 50 MG AND 100 MG TABLETS
PL 18909/0126-7

UKPAR

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ACARBOSE 50 MG AND 100 MG TABLETS
PL 18909/0126-7

LAY SUMMARY

On 01 November 2010, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Arrow Generics Limited licences for the medicinal products Acarbose 50 mg and 100 mg Tablets. This medicine is only available on a prescription from your doctor.

This medicine used to treat diabetes when diet alone, or in combination with other medicines, does not work well enough.

The active ingredient is acarbose. Acarbose helps to control sugar in the bloodstream by regulating the absorption of sugar from food.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Acarbose 50 mg and 100 mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.

ACARBOSE 50 MG AND 100 MG TABLETS
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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Arrow Generics Limited, Marketing Authorisations for the medicinal products Acarbose 50 mg and 100 mg Tablets (PL 18909/0126-7) on 01 November 2010. The products are prescription-only medicines (POM) recommended for the treatment of non-insulin dependent diabetes mellitus (NIDDM) in patients inadequately controlled on diet alone, or on diet and oral hypoglycaemic agents.

Acarbose is a competitive inhibitor of intestinal alpha glucosidases. It delays the digestion and absorption of starch and sucrose. Acarbose has a small, but significant, effect in lowering blood glucose and is used either on its own or as an adjunct to metformin, or to sulphonylureas when they prove inadequate. Postprandial hyperglycaemia in type 1 (insulin-dependent) diabetes can be reduced by acarbose, but it is little used for this purpose.

No pharmacokinetic bioequivalence data were submitted to support these applications because of the low systemic bioavailability of the active substance acarbose – the therapeutic activity of acarbose is within the gastrointestinal tract. Instead, a pharmacodynamic study comparing change in blood glucose and serum insulin for the 100 mg strength of product versus its UK reference product (Glucobay 100 mg Tablets) was submitted. The pharmacodynamic study was carried out in accordance with Good Clinical Practice (GCP).

No new or unexpected safety concerns were raised during the assessment of these applications and it was, therefore, judged that the benefits of taking Acarbose 50 mg and 100 mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

INN: Acarbose

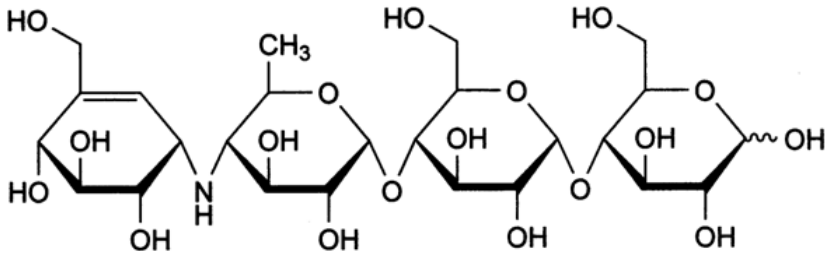
Chemical Name: O-4,6-didesoxy-4-[(1S,4R,5S,6R)-4,5,6,trihydroxy-3-hydroxy-methyl-2-cyclohexene-1-amino]-α-D-glycopyranosyl-(1-4)-α-D-glycopyranosyl-(1-4)-D-glycopyranose

O-4,6-didesoxy-4-[[(1S,4R,5S,6S)-4,5,6,trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl]amino]-α-D-glucopyranosyl-(1-4)-O-α-D-glucopyranosyl-(1-4)-α-D-glucose

O-4,6-didesoxy-4-[[(1α,4α,5β,6α)-4,5,6,trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl]amino]-α-D-glucopyranosyl-(1-4)-O-α-D-glycopyranosyl-(1-4)-D-glucose

Molecular Formula: $C_{25}H_{43}NO_{18}$

Structure:



Molecular weight: 645.63

Appearance: A hygroscopic white to off-white amorphous powder, odourless and slightly sweet. It is freely soluble in water and in methanol, slightly soluble in ethanol and practically insoluble in acetone and acetonitrile.

Acarbose is the subject of a European Pharmacopoeia monograph

All aspects of the manufacture and control of the active substance acarbose are either covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability, or by information provided by the applicant and the relevant active substance supplier.

Appropriate stability data have been generated to support a suitable retest period for the active substance when stored in the proposed packaging.

MEDICINAL PRODUCT

Other ingredients

Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose, maize starch, croscarmellose sodium, colloidal anhydrous silica and magnesium stearate. Appropriate justifications for the inclusion of each excipient have been provided.

All excipients comply with their respective European Pharmacopoeia monograph. Suitable batch analysis data have been provided for each excipient, showing compliance with their respective monograph/specification.

None of the excipients contain materials of animal or human origin.

Pharmaceutical Development
The objective of the development programme was to formulate products containing 50mg and 100mg acarbose that would be pharmaceutically and therapeutically equivalent to Glucobay 50 mg and 100 mg Tablets (Bayer plc, UK).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process
A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation on batches of each strength has been provided.

Finished product specification
The finished product specifications are satisfactory. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Container Closure System
All strengths of the tablets are packaged in polyvinylchloride/Aclar®/aluminium blisters in pack sizes of 10, 21, 30, 42, 84, 90, 100, 105, 420 and 500 tablets.

Not all pack sizes may be marketed. However, the Marketing Authorisation Holder has committed to submitting mock-ups for approval before marketing any pack size.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials suitable for contact with food.

Stability of the Product
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years, with the storage conditions, “Store in the original package in order to protect from light.”

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the pharmacodynamic study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Forms
The MAA forms are satisfactory.

Expert Report
The pharmaceutical expert report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossiers.

Conclusion
The grant of Marketing Authorisations is recommended.

NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY

No new non-clinical data were submitted, which is acceptable given that therapeutic equivalence to the reference product can be established via the pharmacodynamic study.

NON-CLINICAL EXPERT REPORT

The non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the non-clinical aspects of the dossier.

CONCLUSION

The grant of Marketing Authorisations is recommended.

CLINICAL ASSESSMENT

PHARMACOKINETICS

No new pharmacokinetic data were submitted or required for these applications. As the active substance acarbose has a low systemic bioavailability – the therapeutic activity of acarbose is within the gastrointestinal tract and not systemic – a pharmacokinetic study was considered unnecessary. Instead, the below pharmacodynamic study was submitted to support these applications.

PHARMACODYNAMICS

In support of these applications the Marketing Authorisation Holder has submitted the following pharmacodynamic study:

A randomised, open-label, single-dose, six-sequence, three-period crossover study comparing the pharmacodynamic activity (change in blood glucose and serum insulin) of the test product Acarbose 100 mg Tablets (Arrow Generics Limited) versus the reference product Glucobay 100 mg Tablets (Bayer plc, UK) versus a baseline control of sucrose solution alone in healthy adult subjects.

Subjects were dosed on three separate occasions with either test or reference product, each time just after drinking a sucrose solution, or with a baseline control of sucrose solution alone. Blood glucose (primary variable) and serum insulin (secondary variable) concentrations were measured pre- and up to 4 hours post dose. Each single-dose treatment period was separate by a washout period of 1 week.

The main parameters and statistical evaluation of blood glucose (GLU) and serum insulin (ISL) are presented below (N =35):

Variable	Units	Geometric Mean ±Standard Deviation		
		Acarbose 100mg (Test)	Glucobay 100mg (Reference)	Baseline
GLU C_{max}	mmol/L	7.07 ± 1.0	7.03 ± 1.2	8.0 ±1.1
GLU AUC_{0-4}	mmol/L.h	21.1 ±2.0	21.29±2.3	22.2±2.7
ISL C_{max}	mU/l	41.0±23.0	39.5±22.1	60.1± 36.0
ISL AUC_{0-4}	mU/L.h	52.7±23.5	55.1±31.91	76.0± 42.0

Variable	P-value (formulation difference) Test vs. Reference	P-value (formulation difference) Test vs. Baseline	P-value (formulation difference) Reference vs. Baseline	90% confidence Interval (ratio of means) Test vs. Reference
GLU C_{max}	0.7372	‹0.0001	‹0.0001	0.970 - 1.052
GLU AUC0-4	0.6547	0.0033	0.0114	0.970 - 1.019
ISL Cmax	0.6016	0.0003	‹0.0001	0.899 - 1.227
ISL AUC_{0-4}	0.7617	‹0.0001	0.0002	0.868 - 1.105

The 90% confidence intervals of the measured pharmacokinetic variables fall within the predefined acceptance limits. Although the applicant has used 90% confidence intervals instead of the recommended 95% confidence intervals for statistical evaluation of the pharmacodynamic study data, it is unlikely that using the latter would significantly impact the outcome of the study findings or conclusion.

The applicant has submitted an adequate justification for the results and conclusions from the pharmacodynamic study with the 100mg tablet strength to be extrapolated to the 50mg tablet strength.

EFFICACY
No new efficacy data were submitted or required for these applications.

SAFETY
No new data on the safety are required for these types of applications. However the applicant has provided several copies of publications with a safety review from the literature. No new safety issues have been detected.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELS
The SmPCs, PIL and labels are medically acceptable. The SmPCs are consistent with those for the originator products.

CLINICAL EXPERT REPORT
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossiers.

CONCLUSION
The grant of Marketing Authorisations is recommended.

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Acarbose 50 mg and 100 mg Tablets, are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the risk-benefit balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY

With the exception of the pharmacodynamic study, no new data were submitted and none are required for applications of this type.

The submitted pharmacodynamic study demonstrated that the applicant's Acarbose 100 mg Tablets can be considered equivalent to the reference product, Glucobay 100 mg Tablets (Bayer plc, UK). A suitable justication was provided for extrapolating the results from this study to the 50 mg strength tablets.

SAFETY

The safety profile of acarbose is well-known. No new or unexpected safety concerns arose from these applications.

PRODUCT LITERATURE

The approved SmPCs are satisfactory and consistent with those for the reference products. The final PIL and labelling texts are satisfactory and consistent with those for the reference products and the approved SmPCs.

BENEFIT-RISK ASSESSMENT

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data provided support the claim that these products can be considered equivalent to the reference products, Glucobay 50 mg and 100mg Tablets (Bayer plc, UK). Extensive clinical experience with acarbose is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

ACARBOSE 50MG AND 100MG TABLETS
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STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation applications on 10 January 2005
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 03 October 2005.
3	Following assessment of the application the MHRA requested further information relating to the clinical dossiers on 11 June 2008, and the quality dossiers on 21 October 2005 and 18 June 2010.
4	The applicant responded to the MHRA's requests, providing further information on the clinical dossiers on 30 December 2008 and the quality dossiers on 30 December 2008 and 22 September 2010
5	The applications were determined on 01 November 2010

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 a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.

Acarbose 50 mg Tablets are off-white, round, convex tablets with 'AR' over '50' on one side and '>' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Indications

Acarbose Tablets are recommended for the treatment of non-insulin dependent (NIDDM) diabetes mellitus in patients inadequately controlled on diet alone, or on diet and oral hypoglycaemic agents.

Mode of action

Acarbose is a competitive inhibitor of intestinal alpha-glucosidases with maximum specific inhibitory activity against sucrase. Acarbose dose-dependently delays the digestion of starch and sucrose into absorbable monosaccharides in the small intestine. In patients with diabetes, this results in a lowering of postprandial hyperglycaemia and a smoothing effect on fluctuations in the daily blood glucose profile.

In contrast to sulphonylurea drugs, acarbose has no stimulatory action on the pancreas.

Treatment with Acarbose Tablets 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.

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

4.2 Posology and method of administration

Acarbose Tablets are administered 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.

Adults

The recommended initial dose is 50mg three times a day. However, some patients may benefit from a more gradual initial dose titration to minimise gastrointestinal side-effects. This may be achieved by initiating treatment at 50mg once or twice a day, with subsequent titration to a three times a day regimen.

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

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 judgment of the prescriber.

Acarbose is intended for continuous long-term treatment.

Elderly patients
No modification of the normal adult dosage regimen is necessary.

Children and adolescents under 18 years
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.

4.3 Contraindications

- Hypersensitivity to acarbose or any of the excipients
- Use during pregnancy and in nursing mothers.

Acarbose Tablets are also contra-indicated in patients with colonic ulceration, inflammatory bowel disease, partial intestinal obstruction or in patients predisposed to intestinal obstruction.

In addition, Acarbose Tablets 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.

Acarbose Tablets are contra-indicated in patients with 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 of less than 25 ml/min/1.73m².

4.4 Special warnings and precautions for use

Hypoglycaemia: When administered alone, acarbose 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 changed 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 of 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 six to twelve months of treatment. If elevated transaminases are observed, 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 medicinal products and other forms of interaction

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 gastro-intestinal side-effects. If the symptoms are severe, a temporary dose reduction of acarbose may be warranted.

The concomitant administration of cholestyramine may enhance the effects of Acarbose Tablets, particularly with respect to reducing postprandial insulin levels. Simultaneous administration of acarbose and cholestyramine should, therefore, 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.

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 Pregnancy and lactation

The use of acarbose is contra-indicated in pregnancy and in nursing mothers.

The safety of this medicinal product 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.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable 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 trial 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 during postmarketing surveillance only (status: 31 Dec 2005) 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					***Allergic reaction (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 liver enzymes***	***Jaundice***	***Hepatitis***

<The MedDRA preferred term is used to describe a certain reaction and its synonyms and related conditions. ADR term representation is based on MedDRA version 11.1. >

In addition, events reported as liver disorder, hepatic function abnormal and liver injury have been received, particularly 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, clinically relevant abnormal liver function tests (three times above upper limit of normal range) were rarely observed. Abnormal values may be transient under ongoing therapy with acarbose. (See Section 4.4).

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 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.

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 (200mg) 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 hours. 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 comprised two peaks. The first peak, with an average acarbose-equivalent concentration of 52.2 ± 15.7µg/l after 1.1 ± 0.3 h, is in agreement with corresponding data for the concentration course of the inhibitor substance (49.5 ± 26.9µg/l after 2.1 ± 1.6 h). The second peak is on average 586.3 ± 282.7µg/l and is reached after 20.7 ± 5.2 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 ± 2.7 h for the distribution phase and 9.6 ± 4.4 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

Acute toxicity

LD_{50} studies were performed in mice, rats and dogs. Oral LD_{50} values were estimated to be >10g/kg body-weight. Intravenous LD_{50} values ranged from 3.8g/kg (dog) to 7.7g/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 450mg/kg body-weight were tolerated without drug-related toxicity.

In the dog study, daily doses of 50-450mg/kg were associated with decreases in body-weight. This occurred due to the fact that dosing of the animals took place shortly before their 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 4500ppm acarbose in their feed, no drug-related toxicity was observed. In dogs, also treated for one year with daily doses of up to 400mg/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 studies

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 540mg/kg/day. The oral administration of up to 540mg/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
Cellulose, Microcrystalline
Maize Starch
Croscarmellose Sodium
Silica, Colloidal Anhydrous
Magnesium Stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store in the original package in order to protect from light.

6.5 Nature and contents of container
PVC/Aclar®/Aluminium blisters containing 10, 21, 30, 42, 84, 90, 100, 105, 420 and 500 tablets.*

* Not all pack sizes may be marketed

6.6 Special precautions for disposal
Not relevant.

7 MARKETING AUTHORISATION HOLDER
Arrow Generics Limited
Unit 2, Eastman Way,
Stevenage
Hertfordshire
SG1 4SZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 18909/0126

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
01/11/2010

10 DATE OF REVISION OF THE TEXT
01/11/2010

1 NAME OF THE MEDICINAL PRODUCT

Acarbose 100 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg acarbose.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.

Acarbose 100 mg Tablets are an off-white, round, convex tablet, with 'AR' scoreline '100' on one side and '>' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Indications

Acarbose Tablets are recommended for the treatment of non-insulin dependent (NIDDM) diabetes mellitus in patients inadequately controlled on diet alone, or on diet and oral hypoglycaemic agents.

Mode of action

Acarbose is a competitive inhibitor of intestinal alpha-glucosidases with maximum specific inhibitory activity against sucrase. Acarbose dose-dependently delays the digestion of starch and sucrose into absorbable monosaccharides in the small intestine. In patients with diabetes, this results in a lowering of postprandial hyperglycaemia and a smoothing effect on fluctuations in the daily blood glucose profile.

In contrast to sulphonylurea drugs, acarbose has no stimulatory action on the pancreas.

Treatment with Acarbose Tablets 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.

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

4.2 Posology and method of administration

Acarbose Tablets are administered 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.

Adults

The recommended initial dose is 50mg three times a day. However, some patients may benefit from a more gradual initial dose titration to minimise gastrointestinal side-effects. This may be achieved by initiating treatment at 50mg once or twice a day, with subsequent titration to a three times a day regimen.

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

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 judgment of the prescriber.

Acarbose is intended for continuous long-term treatment.

Elderly patients
No modification of the normal adult dosage regimen is necessary.

Children and adolescents under 18 years
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.

4.3 Contraindications

- Hypersensitivity to acarbose or any of the excipients
- Use during pregnancy and in nursing mothers.

Acarbose Tablets are also contra-indicated in patients with colonic ulceration, inflammatory bowel disease, partial intestinal obstruction or in patients predisposed to intestinal obstruction.

In addition, Acarbose Tablets 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.

Acarbose Tablets are contra-indicated in patients with 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 of less than 25 ml/min/1.73m².

4.4 Special warnings and precautions for use

Hypoglycaemia: When administered alone, acarbose 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 changed 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 of 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 six to twelve months of treatment. If elevated transaminases are observed, 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 medicinal products and other forms of interaction

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 gastro-intestinal side-effects. If the symptoms are severe, a temporary dose reduction of acarbose may be warranted.

The concomitant administration of cholestyramine may enhance the effects of Acarbose Tablets, particularly with respect to reducing postprandial insulin levels. Simultaneous administration of acarbose and cholestyramine should, therefore, 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.

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 Pregnancy and lactation

The use of acarbose is contra-indicated in pregnancy and in nursing mothers.

The safety of this medicinal product 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.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable 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 trial 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 during postmarketing surveillance only (status: 31 Dec 2005) 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					***Allergic reaction (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 liver enzymes***	***Jaundice***	***Hepatitis***

< The MedDRA preferred term is used to describe a certain reaction and its synonyms and related conditions. ADR term representation is based on MedDRA version 11.1. >

In addition, events reported as liver disorder, hepatic function abnormal and liver injury have been received, particularly 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, clinically relevant abnormal liver function tests (three times above upper limit of normal range) were rarely observed. Abnormal values may be transient under ongoing therapy with acarbose. (See Section 4.4).

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 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.

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 (200mg) 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 hours. 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 comprised two peaks. The first peak, with an average acarbose-equivalent concentration of 52.2 ± 15.7µg/l after 1.1 ± 0.3 h, is in agreement with corresponding data for the concentration course of the inhibitor substance (49.5 ± 26.9µg/l after 2.1 ± 1.6 h). The second peak is on average 586.3 ± 282.7µg/l and is reached after 20.7 ± 5.2 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 ± 2.7 h for the distribution phase and 9.6 ± 4.4 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

Acute toxicity

LD_{50} studies were performed in mice, rats and dogs. Oral LD_{50} values were estimated to be >10g/kg body-weight. Intravenous LD_{50} values ranged from 3.8g/kg (dog) to 7.7g/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 450mg/kg body-weight were tolerated without drug-related toxicity.

In the dog study, daily doses of 50-450mg/kg were associated with decreases in body-weight. This occurred due to the fact that dosing of the animals took place shortly before their 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 4500ppm acarbose in their feed, no drug-related toxicity was observed. In dogs, also treated for one year with daily doses of up to 400mg/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 studies
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 540mg/kg/day. The oral administration of up to 540mg/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

Cellulose, Microcrystalline
Maize Starch
Croscarmellose Sodium
Silica, Colloidal Anhydrous
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

PVC/Aclar®/Aluminium blisters containing 10, 21, 30, 42, 84, 90, 100, 105, 420 and 500 tablets.*

* Not all pack sizes may be marketed

6.6 Special precautions for disposal

Not relevant.

7 MARKETING AUTHORISATION HOLDER

Arrow Generics Limited
Unit 2, Eastman Way,
Stevenage
Hertfordshire
SG1 4SZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 18909/0127

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/11/2010

10 DATE OF REVISION OF THE TEXT

01/11/2010

PACKAGE LEAFLET: INFORMATION FOR THE USER

Acarbose 50 & 100 mg Tablets

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT ACARBOSE IS AND WHAT IT IS USED FOR

Acarbose belongs to a group of medicines called 'alpha glucosidase inhibitors' which are used to treat **non-insulin dependent diabetes**.

Acarbose works by controlling your blood sugar levels. This is achieved by slowing down the digestion of carbohydrates (complex sugars) in your food into simpler sugars and therefore reduces the high blood sugar levels which can occur after each meal.

Acarbose can be used to treat diabetes when a restricted diet alone or in combination with other sugar-lowering medicines does not work well enough.

2. BEFORE YOU TAKE ACARBOSE TABLETS

Do not take Acarbose Tablets:
- if you are allergic (hypersensitive) to acarbose
- if you are allergic to any of the other ingredients in the tablets (see section 6 – Further information)
- you are pregnant, likely to become pregnant or are breast-feeding
- you are suffering from inflammation or ulceration of the bowel e.g. ulcerative colitis or Crohn's disease
- you have or are susceptible to an obstruction in your intestines (gut)
- you have trouble digesting or absorbing food properly due to a problem with your gut
- you have a large hernia or any other condition where increased gas in your gut may make your condition worse
- you have liver disease
- you have severe kidney disease.

Take special care with Acarbose Tablets
As a diabetic you may also be receiving other treatments for your diabetes. If you are taking insulin or certain medicines (e.g. glibenclamide or chlorpropamide) to control your blood sugar, you will probably be used to avoiding hypoglycaemic episodes ('hypos') by taking sugar when you feel that your blood sugar level is too low.

When taking acarbose, **do not** treat a hypoglycaemic episode with ordinary sugar (sucrose). You must instead take some **glucose** (also known as dextrose) in the form of tablets, syrup, or sweets which should be available from your local pharmacist.

Acarbose Tablets may also affect the levels of certain proteins called enzymes in your blood. Your doctor may wish to see you more often to monitor the levels of these enzymes particularly in the first year of your treatment.

Taking other medicines
Tell your doctor if you are already taking any of the following as they may interact with your medicine. Your doctor may therefore need to adjust the dose of acarbose or the other medicine:
- medicines known as 'intestinal adsorbents' such as charcoal, as these can reduce the effect of acarbose
- medicines to aid digestion containing digestive enzymes (e.g. amylase), as these can reduce the effect of acarbose
- neomycin (an antibiotic), as this can increase the side-effects acarbose can cause
- cholestyramine (used for the treatment of high cholesterol), as this can increase the effect of acarbose
- digoxin (used for the treatment of heart failure), as acarbose can alter its effect.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Acarbose Tablets with food and drink
As you will be on a restricted diet, do not take food or drinks containing carbohydrates (including ordinary sugar (sucrose)) at the same time as your tablets as this can lead to diarrhoea, wind and stomach pain.

You should always follow your doctor's advice on your diet.

Pregnancy and breast-feeding
Do not take Acarbose Tablets if you are pregnant, think you may be pregnant or are breast-feeding. If you think you may have become pregnant whilst taking these tablets, you should contact your doctor as soon as possible.

Ask your doctor or pharmacist for advice before taking any medicine.

3. HOW TO TAKE ACARBOSE TABLETS

Always take Acarbose Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

It is important that you take your tablets at the start of a meal and not at any other time. They should preferably be chewed with the first mouthful of food. If you prefer not to chew your tablets they should be swallowed whole with a little liquid **immediately** before your meal.

Dosage:
The usual starting dose is one 50 mg tablet taken three times a day with meals. However at the start of the treatment your doctor may recommend that you take your tablets once or twice a day before increasing the dose to three times a day.

Six to eight weeks after the start of the treatment your doctor may decide to increase your dose depending on how the tablets are working. You should be aware that acarbose is intended for long-term treatment.

To gain the maximum benefit from your Acarbose Tablets you should adhere to the diet prescribed by your doctor. This should also help in reducing any side effects you may experience. If any distressing side effects develop in spite of strict adherence to your diet, contact your doctor as your dose of acarbose may need to be reduced.

Use in children:
Acarbose Tablets are not recommended for children and adolescents under the age of 18 years.

If you take more Acarbose Tablets than you should, you may suffer from flatulence (wind), stomach pain and diarrhoea especially if you take the tablets with food and drink containing carbohydrates. If you take too many tablets, you should contact your doctor immediately or go to the nearest casualty department. Remember to take the pack and any remaining tablets with you.

If you forget to take your Acarbose Tablets, simply take your next dose on time. Do not take the missed dose or a double dose to make up for the one you missed. **Do not take the tablets between meals.**

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Acarbose Tablets can cause side effects, although not everybody gets them.

If you get any of the following side effects you should stop taking your tablets and tell your doctor immediately:
- **swelling of the lips, face and tongue, difficulty in breathing, feeling faint, rash or itching (affecting the whole body)**
- **unusual bruising, nosebleeds or bleeding gums**
- **your skin or eyes start turning yellow or you have severe stomach ache.**

The following side effects have been reported:

Very common side effects (probably affecting more than 1 in 10 people):
- flatulence (wind)*

Common side effects (probably affecting fewer than 1 in 10 people):
- diarrhoea*
- stomach pain*

Uncommon side effects (probably affecting fewer than 1 in 100 people):
- nausea and vomiting (feeling and being sick)*
- indigestion*
- increase in liver enzymes

Rare side effects (probably affecting fewer than 1 in 1,000 people):
- swelling
- jaundice (yellowing of the skin and eyes)

Other side effects (frequency unknown):
- a decrease in the number of blood cells needed for clotting (thrombocytopenia)
- inflammation of the liver (hepatitis)
- allergic reactions
- gas pockets in the bowel
- a decrease in bowel activity

* Do not take indigestion (antacid) preparations for the treatment of these symptoms as they have been shown to have no effect. If your symptoms persist for more than 2-3 days or if they are severe, please consult your doctor, especially in the case of diarrhoea.

In addition, side effects including liver disorder, abnormal liver function and liver injury have been reported. Individual cases of severe liver infection have also been reported, but it is not clear whether these are as a result of taking acarbose.

Blood tests have sometimes shown an increase in liver enzymes in patients taking acarbose. If you are having a test on your liver you should inform the doctor that you are taking acarbose.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ACARBOSE TABLETS

Keep out of the reach and sight of children.

Do not use Acarbose Tablets after the expiry date which is stated on the blister and carton after EXP:. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Acarbose Tablets contain:
- The active substance is acarbose (each tablet contains 50 or 100mg of acarbose)
- The other ingredients are microcrystalline cellulose, maize starch, croscarmellose sodium, colloidal silica anhydrous and magnesium stearate.

What Acarbose Tablets look like and contents of the pack

Your medicine is in the form of round, convex tablets.
- The 50 mg tablets are off-white with 'AR' over '50' on one side and '>' on the other side.
- The 100 mg tablets are off-white with 'AR' scoreline '100' on one side and '>' on the other side.

Acarbose Tablets are available in blister packs of 10, 21, 30, 42, 84, 90, 100, 105, 420 & 500 tablets (not all pack sizes may be marketed).

Marketing Authorisation Holder
Arrow Generics Limited
Unit 2, Eastman Way, Stevenage, SG1 4SZ, United Kingdom.

Manufacturer:
Arrow Pharm (Malta) Limited
62 Hal Far Industrial Estate, Birzebbugia, BBG3000, Malta.

This leaflet was last approved in 09/2010

LFT0052AA

Labelling


Space for pharmacist's label:
5 060034 833949 >
For oral use.
Read the package leaflet before use.
Store in the original package in order to protect from light.
Keep out of the reach and sight of children.
POM
PL 18909/0126
Marketing Authorisation Holder:
Arrow Generics Limited, Unit 2, Eastman Way, Stevenage, Herts, SG1 4SZ, United Kingdom
LOT:
EXP:
Acarbose 50mg Tablets
90 tablets
arrow GENERICS
CAR/204AA
Acarbose 50mg Tablets
90 tablets
Each tablet contains 50mg of acarbose.

Acarbose 50mg Tablets
Arrow Generics Limited
R301194A


Space for pharmacist's label:
5 060034 833956 >
For oral use.
Read the package leaflet before use.
Store in the original pack age in order
to protect from light.
Keep out of the reach and sight of children.
PL 18909/0127
Marketing Authorisation Holder:
Arrow Generics Limited, Unit 2, Eastman Way,
Stevenage, Herts, SG1 4SZ, United Kingdom
POM
LOT:
EXP:
Acarbose 100mg Tablets
90 tablets
arrow GENERICS
CAR0205AA
Acarbose 100mg Tablets
90 tablets
Acarbose 100mg Tablets
90 tablets
arrow GENERICS
Each tablet contains 100mg of acarbose.
Acarbose 100mg Tablets
90 tablets
arrow GENERICS
APPROVED
Technic
.pdf saved to fi

Acarbose 100mg Tablets
Arrow Generics Limited
R307DAA