Public Assessment Report

Decentralised Procedure

Acarbose 50mg and 100mg Tablet

Acarbose

UK/H/1218/01-02/DC

UK licence no: PL 19514/0003-4

Applicant: Tecnimede SA
LAY SUMMARY

On the 18th December 2009, the MHRA granted Tecnimed-Sociedade Tecnico-Medicinal S.A Marketing Authorisations (licences) for the medicinal products Acarbose 50 and 100mg Tablets. These are prescription-only medicines (POM).

Acarbose is used in the treatment of non-insulin dependent diabetes mellitus in patients inadequately controlled on diet alone, or on diet and oral hypoglycaemic agents. Acarbose will help to control blood sugar levels. This is because acarbose works by slowing down the digestion of carbohydrates (complex sugars) from your diet, and this reduces the abnormally high blood sugar levels that occur after each meal.

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

Module 1: Information about initial procedure          Page 4
Module 2: Summary of Product Characteristics        Page 5
Module 3: Product Information Leaflet              Page 15
Module 4: Labelling                                 Page 19
Module 5: Scientific Discussion                    Page 35

I. Introduction
II. Quality aspects
III. Non-clinical aspects
IV. Clinical aspects
V. Overall conclusion and Benefit-Risk Assessment

Module 6  Steps taken after initial procedure
### Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Acarbose 50 mg and 100 mg Tablets</th>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Article 10.3 hybrid application</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Acarbose</td>
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<tr>
<td><strong>Form</strong></td>
<td>Tablet</td>
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<tr>
<td><strong>Strength</strong></td>
<td>50 mg, 100mg</td>
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</tbody>
</table>
| **MA Holder** | Tecnimede – Sociedade Técnico-Medicinal SA  
Rua da Tapada Grande, nº2  
Abrunheira, 2710-089 Sintra, Portugal |
| **RMS** | UK |
| **CMS** | EL, HU, IE, IT, LU, NL, PL, RO, SI |
| **Procedure Number** | UK/H/1218/01-02/DC |
| **Timetable** | Day 210 – 22<sup>nd</sup> November 2009 |
Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Acarbose 50 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 50 mg of Acarbose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.

White, plain, round tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Acarbose is recommended for the treatment of type II diabetes mellitus in patients inadequately controlled on diet alone, or on diet and oral hypoglycaemic agents.

4.2 Posology and method of administration
Acarbose 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.

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

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

Patients receiving the maximum dose require careful monitoring (see Special warnings and precautions for use, Section 4.4).

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.

Renal or hepatic impairment
See section 4.3.

4.3 Contraindications
Hypersensitivity to acarbose or any of the excipients. Acarbose is also contra-indicated in patients with inflammatory bowel disease, colonic ulceration, partial intestinal obstruction or in patients predisposed to intestinal obstruction. In addition, 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 is 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 < 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 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 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

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 colestyramine may enhance the effects of Acarbose, particularly with respect to reducing postprandial insulin levels. Simultaneous administration of Acarbose and colestyramine should, therefore, be avoided. In the rare circumstance that both Acarbose and colestyramine therapy are withdrawn simultaneously, care is needed as a rebound phenomenon has been observed with respect to insulin levels in non-diabetic subjects.

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

In a pilot study to investigate a possible interaction between Acarbose and nifedipine, no significant or reproducible changes were observed in the plasma nifedipine profiles.

4.6 Pregnancy and lactation

Pregnancy
For acarbose, no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition or postnatal development (see section 5.3).

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 fetal malformations associated with abnormal blood glucose levels.

Lactation
It is unknown whether acarbose is excreted in human breast milk. Animal studies have shown excretion of acarbose in breast milk. Acarbose should not be used during breast-feeding.

4.7 Effects on ability to drive and 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 other antidiabetic agents.

4.8 Undesirable effects
Adverse drug reactions (ADRs) 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 listed below.
ADRs derived from post marketing reports (status: 31 Dec 2005) are printed in bold italic.

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<td>Thrombocytopenia</td>
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<td>Gastrointestinal disorders (1)</td>
<td>Flatulence</td>
<td>Diarrhoea</td>
<td>Nausea</td>
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<td>Ileus</td>
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<td></td>
<td>Borborygmi</td>
<td>Abdominal pain</td>
<td>Vomiting</td>
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<td>Subileus</td>
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<td></td>
<td>Abdominal distension</td>
<td></td>
<td></td>
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<td>Constipation</td>
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<td>Hepatobiliary disorders (2)</td>
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<td>Liver enzyme increase</td>
<td></td>
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<td>Skin and subcutaneous tissue disorders</td>
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(1) Diarrhoea and abdominal pain may occur after sucrose-containing foods are ingested. If the prescribed diabetic diet is not observed the gastrointestinal adverse events may be intensified. The symptoms are related both to the dose and to the dietary substrate and may diminish with continued treatment. If severe symptoms develop in spite of adherence to the prescribed diabetic diet the dose must be temporarily or permanently reduced. Often the dose reduction is sufficient for one of the main meals (lunch or dinner). Should diarrhoea persist, then patients should be closely monitored and the dosage reduced or therapy withdrawn, if necessary.

(2) Rarely, clinically significant abnormal hepatic function tests (three times above the upper limit for normal values) have been observed in patients treated with the recommended daily dose of 150mg to 300mg of acarbose daily. Abnormal values may be transient during treatment (see section 4.4).

If ileus or subileus is suspected, treatment must be stopped immediately. In Japan, individual cases of fulminant liver failure have been observed, although the role of acarbose is unclear.

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 Acarbose therapy. (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: A10B F01.

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 (200 mg) 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 h. 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 was comprised of two peaks. The first peak, with an average acarbose-equivalent concentration of $52.2 \pm 15.7 \mu g/l$ after $1.1 \pm 0.3$ h, is in agreement with corresponding data for the concentration course of the inhibitor substance ($49.5 \pm 26.9 \mu g/l$ after $2.1 \pm 1.6$ h). The second peak is on average $586.3 \pm 282.7 \mu g/l$ and is reached after $20.7 \pm 5.2$ 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 $3.7 \pm 2.7$ h for the distribution phase and $9.6 \pm 4.4$ 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
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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Microcrystalline cellulose
Colloidal anhydrous silica
Magnesium stearate
Pregelatinised starch

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.
6.4 **Special precautions for storage**
Do not store above 30° C. Store in the original packaging to protect from light and moisture.

6.5 **Nature and contents of container**
Transparent and colourless PVC/PCTFE/PVC film/Al foil blisters, packed in outer cartons. is used as container closure system for Acarbose tablets.

Pack sizes: 10, 20, 30, 50, 60, 120 and 270 tablets.

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 **MARKETING AUTHORISATION HOLDER**
TECNIMEDE-- Sociedade Técnico-Medicinal, S.A.
Rua da Tapada Grande, n.º 2
Abrunheira
2710-089 Sintra
Portugal

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 19514/0003

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
18/12/2009

10 **DATE OF REVISION OF THE TEXT**
18/12/2009
1 NAME OF THE MEDICINAL PRODUCT
Acarbose 100 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 100 mg of Acarbose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.

White, plain, round tablets, scored on one side.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Acarbose is recommended for the treatment of type II diabetes mellitus in patients inadequately controlled on diet alone, or on diet and oral hypoglycaemic agents.

4.2 Posology and method of administration
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Adults

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

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

Patients receiving the maximum dose require careful monitoring (see Special warnings and precautions for use, Section 4.4).

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.

Renal or hepatic impairment
See section 4.3.

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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 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.

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Lactation
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<tr>
<td></td>
<td></td>
<td></td>
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### 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: A10B F01.

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 (200 mg) 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 h. 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 was comprised of two peaks. The first peak, with an average acarbose-equivalent concentration of $52.2 \pm 15.7 \, \mu g/l$ after $1.1 \pm 0.3$ h, is in agreement with corresponding data for the concentration course of the inhibitor substance ($49.5 \pm 26.9 \, \mu g/l$ after $2.1 \pm 1.6$ h). The second peak is on average $586.3 \pm 282.7 \, \mu g/l$ and is reached after $20.7 \pm 5.2$ 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 $3.7 \pm 2.7$ h for the distribution phase and $9.6 \pm 4.4$ 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

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Colloidal anhydrous silica

Magnesium stearate

Pregelatinised starch

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30° C. Store in the original packaging to protect from light and moisture.
6.5 Nature and contents of container
Transparent and colourless PVC/PCTFE/PVC film/Al foil blisters, packed in outer cartons. is used as container closure system for Acarbose tablets.

Pack sizes: 10, 20, 30, 50, 60, 120 and 270 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/12/2009

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18/12/2009
Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Acarbose 50 mg Tablets

Acarbose

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 further questions, ask your doctor or your 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 gets 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
2. Before you take Acarbose
3. How to take Acarbose
4. Possible side effects
5. How to store Acarbose
6. Further information

1. WHAT ACARBOSE IS AND WHAT IT IS USED FOR

Acarbose is used in the treatment of non-insulin dependent diabetes mellitus in patients inadequately controlled on diet alone, or on diet and oral hypoglycaemic agents. This medicine has been prescribed for you by your doctor to treat your diabetes. Acarbose will help to control your blood sugar levels. This is because Acarbose works by slowing down the digestion of carbohydrates (complex sugars) from your diet, and this reduces the abnormally high blood sugar levels that occur after each meal.

2. BEFORE YOU TAKE ACARBOSE

Do not take Acarbose

- If you are allergic (hypersensitive) to acarbose or any of the other ingredients of Acarbose. If you are unsure about this ask your doctor.
- If you suffer from inflammation or ulceration of the bowel, e.g. ulcerative colitis or Crohn's disease.
- If you have, or are susceptible to, an obstruction in your intestines.
- If you have a liver disorder.
- If you have an intestinal disease whereby you do not digest or absorb food properly.
- If you have a large haema or any other condition where increased gas in your intestine may make it worse.
- If you are pregnant or breastfeeding.

If you have a kidney disorder, do not take Acarbose without consulting your doctor first.

If you are unsure whether you might have any of these conditions, please ask your doctor.

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

Acarbose is not recommended for patients under 18 years of age.

Take special care with Acarbose

Treating hypoglycaemic episodes ("hypo"). As a diabetic you may also be receiving other treatments for your diabetes.

- If you are taking insulin or sulphonylureas drugs to control your blood sugar, you will probably be used to avoiding hypoglycaemic episodes 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). INSTEAD TAKE SOME GLUCOSE (ALSO KNOWN AS DEXTROSE) TABLETS, SYRUP, OR SWEETS WHICH SHOULD BE AVAILABLE FROM YOUR LOCAL PHARMACIST.

This medicine may affect the levels of certain proteins called enzymes in your blood. Your doctor may wish to see you more frequently in order to monitor the levels of these enzymes.

Using other medicines

Acarbose may alter the effect of other drugs or, alternatively, some drugs may alter the effect of Acarbose. If you are using any of the following drugs, speak to your doctor or pharmacist before taking this medicine:

- Drugs known as intestinal adsorbsents, e.g. charcoal.
- Drugs to help your digestion (digestive enzyme preparations e.g. amylase, pancreatin).
- The antibiotic, neomycin.
- Colestyramine, a drug used to treat high cholesterol.
- Digoxin.

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

Taking Acarbose with food and drink

Acarbose tablets can be swallowed with a little liquid immediately before the meal.

Pregnancy and breast-feeding:

Do not take this medicine if you are pregnant or breast-feeding. If you are taking Acarbose and think that you may be pregnant, or are planning a family, consult your doctor.

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

Driving and using machines:

Acarbose should not affect your ability to drive or operate machinery.

Important information about some of the ingredients of Acarbose

This medicine contains the following excipients: microcrystalline cellulose, pregelatinised starch, colloidal anhydrous silica, and magnesium stearate.

3. HOW TO TAKE ACARBOSE

To gain the maximum benefit from Acarbose you should adhere to the diet prescribed for you by your doctor. This will also help in reducing any side-effects you may experience

Always take Acarbose exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose is...
one or two tablets taken with meals 3 times a day. However, when you first start your treatment, your doctor may recommend that you take your tablets once or twice a day before increasing your dose to three times a day. This medicine is intended for long-term use.

Acarbose tablets should be chewed with the first mouthful of food. If you prefer not to chew the tablets then swallow them whole with a little liquid immediately before the meal.

If you take more Acarbose than you should
If you do exceed the prescribed dose, or in the event of an overdose, you may experience diarrhoea and other intestinal symptoms such as flatulence (wind) and abdominal pain.

If you take more than the prescribed dose, or in the event of an overdose, avoid the intake of carbohydrate-containing food or drinks and seek medical advice immediately. If possible, take your tablets or the pack with you to show the doctor.

If you forget to take Acarbose
If you forget to take one or more doses of Acarbose do not take the tablets between meals but, instead, wait until your next scheduled dose and meal and continue as before.

Do not take a double dose to make up for a forgotten tablet.

4. POSSIBLE SIDE EFFECTS

The frequency of the following effects is unknown and based on isolated reports. However, if you get any of these reactions, seek urgent medical attention.

- A decrease in the the platelet in the blood (associated with rash, easy bruising or bleeding)
- Allergic reactions such as rash, redness of the skin, skin eruptions, itching
- Decrease in bowel activity (ileus associated with severe abdominal pain, vomiting and absence of gas or bowel motions)
- Inflammation of the liver (hepatitis associated with jaundice-yellowing of the skin and eyes)

Like all medicines, Acarbose can cause side effects, although not everybody gets them. During the first few days or weeks of treatment with Acarbose you may experience increased flatulence (wind), rumbling in your stomach, a feeling of fullness and possibly abdominal cramps. It is also possible that you may pass softer stools or even experience diarrhoea, particularly after a meal containing sugar or sucrose-containing foods. Normally, these symptoms will disappear if you continue treatment and keep to your prescribed diet.

The following side effect occurred very commonly (in more than 1 in 10 patients) in clinical trials:
- Flatulence (wind)

The following side effects occurred commonly (in less than 1 in 10 patients but more than 1 per 100 patients) in clinical trials:
- Diarrhoea
- Stomach and abdominal pain

Normally, these symptoms will disappear if you continue treatment and keep to your prescribed diet.

The following side effects occurred uncommonly (in less than 1 in 100 patients but in more than 1 per 1000 patients) in clinical trials:
- Nausea
- Vomiting
- Indigestion
- Transient increase in liver enzymes
- Jaundice (yellowing of the skin)

DO NOT TAKE INDIGESTION (ANTACID) PREPARATIONS FOR TREATING SYMPTOMS OF ABDOMINAL PAIN, DIARRHEA, AND FLATULENCE AS THEY ARE UNLIKELY TO HAVE ANY BENEFICIAL EFFECT. IF YOUR SYMPTOMS PERSIST FOR MORE THAN 2 OR 3 DAYS, OR IF THEY ARE SEVERE, CONSULT YOUR DOCTOR, PARTICULARLY IN THE CASE OF DIARRHOEA.

These effects go away when treatment is stopped.

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

5. HOW TO STORE ACARBOSE

Keep out of the reach and sight of children.

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

Do not store above 30°C. Store in the original packaging. Protect from light and moisture. 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 contains
- The active substance is Acarbose. Each tablet contains 50 mg of Acarbose.
- The other ingredients are microcrystalline cellulose, pregelatinised starch, colloidal anhydrous silica, and magnesium stearate.

What Acarbose looks like and contents of the pack:
White, plain, round tablets.
Acarbose is available as 50 mg tablets in packages of 10, 20, 30, 50, 60, 120 and 270 tablets.

Not all pack sizes may be marketed.

Marketing Authorization Holder and Manufacturer:
Manufacturer: West Pharma Produções Especialidades Farmacêuticas, S.A., Rua João da Deus, nº 11, Venda Nova, 2700 - 486 Amadora, Portugal

This leaflet was last approved in December 2009.
Acarbose 100 mg Tablets

Acarbose

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 further questions, ask your doctor or your 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 gets 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
2. Before you take Acarbose
3. How to take Acarbose
4. Possible side effects
5. How to store Acarbose
6. Further information

1. WHAT ACARBOSE IS AND WHAT IT IS USED FOR

Acarbose is used in the treatment of non-insulin dependent diabetes mellitus in patients inadequately controlled on diet alone, or on diet and oral hypoglycaemic agents. This medicine has been prescribed for you by your doctor to treat your diabetes. Acarbose will help to control your blood sugar levels. This is because Acarbose works by slowing down the digestion of carbohydrates (complex sugars) from your diet, and this reduces the abnormally high blood sugar levels that occur after each meal.

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- Drugs to help your digestion (digestive enzyme preparations e.g. amylase, pancreatic).
- The antibiotic, neomycin.
- Colestevamine, a drug used to treat high cholesterol.
- Digoxin.

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

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Acarbose tablets can be swallowed with a little liquid immediately before the meal.

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Do not take this medicine if you are pregnant or breast-feeding. If you are taking Acarbose and think that you may be pregnant, or are planning a family, consult your doctor.

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- Decrease in bowel activity (ileus associated with severe abdominal pain, vomiting and absence of gas or bowel motions)
- Inflammation of the liver (hepatitis associated with jaundice-yellowing of the skin and eyes)

Like all medicines, Acarbose can cause side effects, although not everybody gets them. During the first few days or weeks of treatment, with Acarbose you may experience increased flatulence (wind), rumbling in your stomach, a feeling of fullness and possibly abdominal cramps. It is also possible that you may pass softer stools or even experience diarrhoea, particularly after a meal containing sugar or sucrose-containing foods. Normally, these symptoms will disappear if you continue treatment and keep to your prescribed diet.

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5. HOW TO STORE ACARBOSE

Keep out of the reach and sight of children.

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

Do not store above 30 °C. Store in the original packaging to protect from light and moisture. 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 contains

- The active substance is Acarbose. Each tablet contains 100 mg of Acarbose.
- The other ingredients are microcrystalline cellulose, pregelatinised starch, colloidal anhydrous silica, and magnesium stearate.

What Acarbose looks like and contents of the pack:

White, plain, round tablets, scored on one side. The score line/break line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Acarbose is available as 100 mg tablets in packages of 10, 20, 30, 50, 60, 120 and 270 tablets.

Not all pack sizes may be marketed.

Marketing Authorization Holder and Manufacturer:
Marketing Authorization Holder:
TECNIMEDE-Sociedade Técnico-Medicinal, S.A.
Rua da Tapada Grande, n.º 2
Abrunheira, 2710-969 Sintra, Portugal

Manufacturer:
West Pharma Produtos Especialidades Farmacêuticas, S.A.
Rua João de Deus, nº 11, Venda Nova
2700 - 486 Amadora
Portugal

This leaflet was last approved in December 2009
Module 4

Labelling
ACARBOSE 50 mg Tablets

Each strip contains 10 mg

ACARBOSE 50 mg Tablets

50 mg

10 tablets

TECNIMEDE

MA Holder:
TECNIMEDE - Sociedade Técnica Médical, S.A.
Rua da Tapada Grande, n.° 2
Abrantes, 2710-089 Sintra
Portugal
PL 1954/0003

POM
PAR Acarbose 50 and 100mg Tablets

ACARBOSE 50 mg Tablets

TECNIMEDE

MA Holder:
TECNIMEDE - Sociedade Técnico-Medical, S.A.
Rua da Tapada Grande, nº 2
Abrantes, 2710-069 Sintra
Portugal
PL18514/30003

ACARBOSE 100 mg Tablets

TECNIMEDE

ACARBOSE #50 mg Tablets
PAR Acarbose 50 and 100mg Tablets

Do not exceed 30c.
Keep out of the reach and sight of children.
Store in the original packaging.
Do not use after the expiry date.

Tecnimeo

MA Holder:
Tecnimeo - Sociedade Técnica-Medicinal, S.A.
Rue da Tapada Grelhe, n° 2
Abrunheiro, 2710-089 Braga
Portugal
PL 1961/4/0003

Tecnimeo
ACARBOSE 100 mg Tablets

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ACARBOSE 100 mg Tablets
Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Acarbose 50mg & 100mg tablets, in the treatment of non-insulin dependent (NIDDM) diabetes mellitus in patients inadequately controlled on diet alone, or on diet and oral hypoglycaemic agents, is approvable.

These are applications made under the decentralised procedure (DCP), according to Article 10.3 of 2001/83 EC, as amended, for hybrid application. These products are claiming to be generic medicinal products of Glucobay 50 and 100 tablets, which were originally granted to Bayer SA in Luxembourg on 28 October 1988. Cross-reference has been made to Glucobay 50 mg and 100 mg tablets for which UK licences, PLs 00010/0171 and 0172, were granted to Bayer plc on 28th June 1993 and 28th May 1993, respectively.

With the UK as the Reference Member State in these Decentralised Procedures, Tecnimed – Sociedade Técnico-Medicinal SA is applying for the Marketing Authorisations for Acarbose 50mg and 100mg Tablets in EL, HU, IE, IT, LU, NL, PL, RO and SI.

No new preclinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.
# ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Acarbose 50 and 100mg Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Acarbose</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>A10BF</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>50 and 100mg Tablets</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/1218/01-02/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States Concerned</td>
<td>EL, HU, IE, IT, LU, NL, PL, RO and SI.</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 19514/0003-4</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Tecnimede-Sociedade Técnico-Medicinal S.A, Zona Industrial da Abrunheira, Rua da Tapada Grande 2, Abrunheira Sintra, PT-2710-089, Portugal</td>
</tr>
</tbody>
</table>
II. QUALITY ASPECTS

DRUG SUBSTANCE

INN: acarbose

Chemical Name:

\[O-4,6\text{-Dideoxy-4-[[1S,4R,5S,6S]-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]}\text{amino}]\text{-\textalpha-D-glucopyranosyl-(1\rightarrow4)-\textalpha-D-glucopyranosyl-(1\rightarrow4)}\text{-D-glucopyranose}\]

Structure:

Molecular Formula: \(C_{25}H_{43}NO_{18}\)

Molecular Weight: 646

Appearance: a white or yellowish, amorphous and hygroscopic powder. Very soluble in water, soluble in methanol, practically insoluble in methylene chloride.

All aspects of the manufacture and control of the active substance acarbose are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability. This certificate is accepted as confirmation of the suitability of acarbose for inclusion in the medicinal product.
DRUG PRODUCT

Other ingredients
Other ingredients consist of the pharmaceutical excipients cellulose microcrystalline, pregelatinised starch, colloidal anhydrous silica and magnesium stearate.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Magnesium stearate is from a vegetable source. None of the other excipients are of human origin.

Pharmaceutical Development
The objective of the development programme was to formulate acarbose tablets containing qualitatively and quantitatively the same active substance as Glucobay 50 and 100mg Tablets (Bayer) and exhibiting the same bioavailability in order to comply with the regulations pertaining to abridged applications.

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.

Manufacture
Satisfactory batch formulae have been provided for the manufacture of all strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished product specification
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container-Closure System
The finished product is packed in Transparent and colourless PVC/PCTFE/PVC film/Al foil blisters in pack sizes of 10, 20, 30, 50, 60, 120 and 270 tablets.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years has been set, with the storage instructions ‘Do not store above 30 degree C’ and ‘Store in the original packaging to protect from light and moisture’.

SPC, PIL, Labels
The SPC, PIL and labels are pharmaceutically acceptable.
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. 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.

**Pharmacovigilance System and Risk Management Plan**

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a risk management plan for these products.

**MAA forms**

The MAA forms are pharmaceutically satisfactory.

**Expert report**

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Conclusion**

It is recommended that Marketing Authorisation is granted for these applications.

---

**III. PRE-CLINICAL ASPECTS**

As the pharmacodynamic, pharmacokinetic and toxicological properties of acarbose are well-known, no further studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

---

**IV. CLINICAL ASPECTS**

**Pharmacodynamics**

To support the application, the applicant has not formally submitted any bioequivalence or pharmacodynamic studies as evidence of bioequivalence. Although, modules 1.5.2 and 2.5 make reference to 2 PD studies based on plasma glucose profiles in the presence of test and reference products, the results of these studies are not applicable to the current application as these were based on a preliminary formulation which has been demonstrated to have different dissolution profiles, and different composition vs. the reference and final formulation.

The applicant has requested a biowaiver claiming

- high solubility of acarbose, and rapid dissolution profiles,
- the same qualitative and quantitative composition of active substance, and pharmaceutical formula as the reference product marketed in Portugal, Glucobay,
- a low risk of therapeutic failure,
- with reference to CPMP/EWP/QWP/1401/98 The Note for guidance on the Investigation of Bioavailability and bioequivalence and the CPMP/EWP/239/95 The note for guidance on the clinical requirements for locally applied, locally acting products containing known constituents.

The biowaiver is considered by the RMS to be justified on the basis:

- The applicant has provided arguments based on the very soluble, locally acting nature of the product, and the discriminatory capability of the dissolution testing, to justify the extension of the biowaiver criteria in section 5.1.1 CPMP/EWP/QWP/1401/98 to acarbose. The results of the dissolution testing between reference and final formulation intended for marketing and the quantitative and qualitative similarities between final and reference formulations strengthen these arguments.

- The applicant also draws on the draft bioequivalence guideline and the highly soluble nature of the product, and the BCS categorisation to justify why an exemption from a clinical study may be possible in the case of locally acting products in solution. These arguments are backed up with safety and efficacy considerations. The justifications are acceptable.

- An adequate rationale for not providing PK studies or using other in vivo methods to demonstrate bioequivalence has been provided based on the unknown correlation of PK values with acarbose dose-effect profile, and the difficulties inherent in measuring levels at the brush border- the site of action. The PD study conducted was also hampered by apparent high variability.

- The applicant has provided convincing arguments that the differences between preliminary and final formulations of the generic Acarbose tablets are such that these results of the failed PD study can be discounted, based on dissolution results of preliminary and final formulation, effects of different levels of excipients, and a discriminating in vitro test.

- Additional detail and data has been provided by the applicant based on the dissolution methodology, sensitivity, validation of the testing process, and how the testing process conforms to guidelines and is sufficiently discriminating, with the difference between final and preliminary formulation being more evident in USP pH 6.8 phosphate buffer medium.

In principle, given the biowaiver for efficacy is considered acceptable with final and reference formulation qualitatively the same and quantitatively very similar, thus excluding different effects on membrane transporters, with ostensible equal levels presenting at the site of any absorption, the biowaiver is also considered acceptable for local and systemic safety.

**Pharmacokinetics**
No data have been provided.

**Clinical Efficacy**
No new data have been submitted and none are required.

**Clinical Safety**
No new data have been submitted and none are required.
Expert Reports
A clinical overall summary, written by an appropriately qualified physician, has been provided and is a satisfactory, non-critical summary of Module 5.

Module 1 – Administrative information
MAA forms
The MAA form is medically satisfactory.

SPC, PIL, Labels
The SPC, PIL and labels are medically acceptable. The SPCs are consistent with those for the originator products.

Conclusion
The medical assessor recommended that marketing authorisation was granted for this product.

V. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Acarbose 50mg and 100mg 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 benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for an application of this type.

EFFICACY
No new or unexpected safety concerns arise from these applications.

The SPC and PIL are satisfactory and consistent with that of the reference product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with acarbose is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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