Public Assessment Report

Decentralised Procedure

ACARBOSE 50 MG TABLETS
ACARBOSE 100 MG TABLETS

Procedure No: UK/H/5049/001-2/DC

UK Licence No: PL 17871/0188-9

Jenson Pharmaceutical Services Limited
Lay summary

On 13 December 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations for the medicinal products Acarbose 50 mg and 100 mg Tablets (PL 17871/0188-9; UK/H/5049/001-2/DC) to Jensen Pharmaceuticals Services Limited. These medicines are only available on prescription from your doctor. Acarbose 50 mg and 100 mg Tablets are indicated in the treatment of non-insulin dependent diabetes mellitus in adult patients aged over 18 years inadequately controlled on diet alone, or on diet and oral hypoglycaemic agents.

The active ingredient, acarbose, belongs to a group of medicines called glucosidase inhibitors. Acarbose helps to control blood sugar levels by slowing down the digestion of carbohydrates (complex sugars) from the 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 mg and 100 mg Tablets outweigh the risks and Marketing Authorisations were granted.
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## Module 1

### Information about the initial procedure

| Product Name(s) | UK/H/5049/001/DC: Acarbose 50 mg Tablets  
|                 | UK/H/5049/002/DC: Acarbose 100 mg Tablets |
| Type of Application(s) | Hybrid, Article 10(3) |
| Active Substance | Acarbose |
| Form | Tablets |
| Strengths | 50 mg and 100 mg |
| MA Holder | Jenson Pharmaceutical Services Ltd, Carradine House, 237 Regent’s Park Road, London, N3 3LF, United Kingdom |
| Reference Member State (RMS) | UK |
| Concerned Member State(s) (CMS) | Ireland |
| Procedure Number(s) | UK/H/5049/001-2/DC |
| Timetable | Day 210 – 24 October 2012 |
Module 2
Summary of Product Characteristics

The current approved UK version of the Summary of Product Characteristics (SmPC) for this product is available on the MHRA website.
Module 3
Patient Information Leaflet

The current approved UK version of the Patient Information Leaflet (PIL) for this product is available on the MHRA website.
Module 4
Labelling
Module 5
Scientific discussion during initial procedure

I. INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Acarbose 50 mg and 100 mg Tablets (PL 17871/0188-9; UK/H/5049/001-2/DC) could be approved. These products are prescription-only medicines (POM) indicated in adults and adolescents aged over 18 years. Acarbose 50 mg and 100 mg Tablets are recommended for the treatment of type II diabetes mellitus in patients inadequately controlled on diet alone, or on diet and oral hypoglycaemic agents.

There are no paediatric formulations available and use in children and adolescents is not recommended.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Ireland as Concerned Member State (CMS). The applications were submitted under Article 10(3) of Directive 2001/83/EC, as amended, as hybrid applications. The reference medicinal products for these applications are Glucor/Glucobay 50 mg and 100 mg tablets (Bayer plc), which were first authorised in the EU on 23 October 1988.

The active ingredient, acarbose, acts locally within the intestinal tract: it is a competitive inhibitor of intestinal alpha-glucosidases, with maximum specific inhibitory activity against sucrase. Under the influence of acarbose, the digestion of starch and sucrose into absorbable monosaccharides in the small intestine is delayed in a dose-dependent manner. Acarbose reduces the post-prandial rise in blood glucose and also reduces fluctuations in blood glucose concentration. In diabetic subjects, this results in a lowering of post-prandial hyperglycaemia and a smoothing effect on the daily blood glucose profile.

No new non-clinical or clinical data have been submitted, which is acceptable given that these are hybrid applications based on originator products that have been in clinical use for over 10 years.

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.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
The RMS and CMS considered that the applications could be approved at the end of the procedure (Day 210) on 24 October 2012. After a subsequent national phase, licences were granted in the UK on 13 December 2012.

II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | UK/H/5049/001/DC: Acarbose 50 mg Tablets  
UK/H/5049/002/DC: Acarbose 100 mg Tablets |
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<td>Name(s) of the active substance (INN)</td>
<td>Acarbose</td>
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| Pharmacotherapeutic classification (ATC code)    | Alpha glucosidase inhibitors  
(ATC code: A10B F01)                                                              |
| Pharmaceutical form and strength(s)              | Tablets; 50 mg and 100 mg                                                       |
| Reference numbers for the Decentralised Procedure | UK/H/5049/001-2/DC                                                              |
| Reference Member State (RMS)                     | United Kingdom                                                                   |
| Concerned Member State (CMS)                     | Ireland                                                                          |
| Marketing Authorisation Number(s)                | PL 17871/0188-9                                                                 |
| Name and address of the authorisation holder      | Jenson Pharmaceutical Services Ltd,  
Carradine House, 237 Regent’s Park Road,  
London, N3 3LF  
United Kingdom                                                                          |

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

INN: Acarbose

Chemical Names: 
$O$-$4,6$-$Dideoxy-4$-$[[15S,4R,5S,6S]$-$4,5,6$-$trihydroxy-3$-$
(hydroxymethyl)cyclohex-2$-$eny]amino]$-$α$-$d$-$glucopyranosyl$-$
(1$→$4)$-$O$-$α$-$d$-$glucopyranosyl$-$(1$→$4)$-$d$-$glucopyranose$

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

Structure:

Molecular mass: 646

Appearance: A white to off-white hygroscopic powder.

Solubility: Very soluble in water, soluble in methanol and insoluble in methylene chloride.

Acarbose is the subject of a European Pharmacopoeia monograph.

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.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients namely colloidal anhydrous silica, maize starch, magnesium stearate and microcrystalline cellulose. Appropriate justifications for the inclusion of each excipient have been provided.
All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Pharmaceutical Development**
The objective of the development programme was to formulate safe, efficacious, stable products that were comparable in performance to the originator products, Glucor/Glucobay Tablets 50 mg and 100 mg (Bayer).

Suitable pharmaceutical development data have been provided for these applications.

Comparative *in-vitro* dissolution and impurity profiles have been provided for these products and their respective reference products.

**Manufacturing Process**
Satisfactory batch formulae have been provided for the manufacture of all strengths of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with pilot-scale batches and has shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation studies on future full-scale production batches.

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

**Container Closure System**
The tablets are packaged in clear Aclar – polyvinylchloride/Aluminium blisters. These are packed into cardboard cartons with Patient Information Leaflets in pack sizes of 90 and 100 tablets.

Not all pack sizes may be marketed.

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

**Stability**
Finished product stability studies were performed in accordance with current guidelines on batches of the finished products packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years and storage conditions of “Store in the original package, in order to protect from moisture.”

This medicinal product does not require any special temperature storage conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of the finished products.
Therapeutic equivalence
Investigation of bioequivalence is not appropriate for these products, as the active substance, acarbose, is highly soluble with limited systemic absorption.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are satisfactory from a pharmaceutical perspective.

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 the leaflet contains.

Marketing Authorisation Application (MAA) Forms
All aspects of the MAA forms are satisfactory from a pharmaceutical perspective.

Expert Report (Quality Overall Summary)
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of Marketing Authorisations is recommended.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of acarbose are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT (NON-CLINICAL OVERVIEW)
The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

ENVIRONMENTAL RISK ASSESSMENT
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As these products are intended for generic substitution with products that are already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
The grant of Marketing Authorisations is recommended.
III.3 CLINICAL ASPECTS
The clinical pharmacology of acarbose is well-known.

No clinical studies have been conducted to support these applications. Essential similarity with the originator product is based on the comparative quality attributes of the product. A biowaiver has been granted in line with the requirements of the Committee for Proprietary Medicinal Products ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/2010).

EFFICACY
The efficacy profile of acarbose is well-known. Efficacy is reviewed in the clinical overview. No new efficacy data have been submitted and none are required for these applications.

SAFETY
The safety profile of acarbose is well-known. The safety profile of acarbose is reviewed in the clinical overview. No new safety data have been submitted with these applications and none are required.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN
The Pharmacovigilance System, as described by the Marketing Authorisation Holder, fulfils the requirements and provides adequate evidence that the Marketing Authorisation Holder 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.

Suitable justification has been provided for not submitting a Risk Management Plan for these products.

SUMMARIES OF PRODUCT CHARACTERISTICS (SmPCs), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPCs, PIL and labelling are acceptable from a clinical perspective. The SmPCs are consistent with those for the reference products. The PIL is consistent with the details in the SmPCs and inline with the current guidelines. The labelling is in line with the current guidelines.

CLINICAL EXPERT REPORT (CLINICAL OVERVIEW)
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

CONCLUSION
The grant of Marketing Authorisations is recommended.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The quality characteristics of products 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 benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of acarbose are well-known, no additional data were required.

EFFICACY
The efficacy profile of acarbose is well-known. Efficacy is reviewed in the clinical overview. No new efficacy data have been submitted and none are required for these applications.

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

PRODUCT LITERATURE
The SmPCs, PILs and labelling are satisfactory, and consistent with those for the reference products, where appropriate, and consistent with current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. 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.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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