PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Metformine HCl/Glibenclamide Sandoz 500 mg/2.5 mg and 500 mg/5 mg film-coated tablets
Sandoz B.V., the Netherlands

metformin (as hydrochloride) / glibenclamide

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

EU-procedure number: NL/H/1545/001-002/DC
Registration number in the Netherlands: RVG 103394,103395

17 March 2010

Pharmacotherapeutic group: combinations of oral blood glucose lowering drugs; metformin and sulfonamides
ATC code: A10BD02
Route of administration: oral
Therapeutic indication: type 2 diabetes in adults, as replacement for previous combination therapy with metformin and glibenclamide in patients whose glycaemia is stable and well-controlled.
Prescription status: prescription only
Date of authorisation in NL: 16 November 2009
Concerned Member States: Decentralised procedure with DE.
Application type/legal basis: Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.
I  INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Metformine HCl/Glibenclamide Sandoz 500 mg/2.5 mg and 500 mg/5 mg film-coated tablets, from Sandoz, B.V.. The date of authorisation was on 16 November 2009 in the Netherlands. The product is indicated for treatment of type 2 diabetes in adults, as replacement for previous combination therapy with metformin and glibenclamide in patients whose glycaemia is stable and well-controlled.

A comprehensive description of the indications and posology is given in the SPC.

Metformin
Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia. Metformin may act via 3 mechanisms:
- reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
- and delay of intestinal glucose absorption.
Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters known to date.

Glibenclamide
Glibenclamide is a second generation sulphonylurea with a medium half-life: it causes lowering of blood glucose by stimulating the release of insulin by the pancreas, this effect being dependent on the presence of functioning beta cells in the islets of Langerhans. The stimulation of insulin secretion by glibenclamide in response to a meal is of major importance.
The administration of glibenclamide to diabetics induces an increase in the postprandial insulin-stimulating response. The increased postprandial responses in insulin and C-peptide secretion persist after at least 6 months of treatment.

Metformin + Glibenclamide
Metformin and glibenclamide have different mechanisms and sites of action, but their action is complementary. Glibenclamide stimulates the pancreas to secrete insulin, while metformin reduces cell resistance to insulin by acting on peripheral (skeletal muscle) and hepatic sensitivity to insulin.
Results from controlled, double blind clinical trials versus reference products in the treatment of type 2 diabetes inadequately controlled by monotherapy with metformin or glibenclamide combined with diet and exercise, have demonstrated that the combination had an additive effect on glucose regulation.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Glucovance 500 mg/2.5 mg and 500 mg/5 mg film-coated tablets (NL license RVG 27245 and 27246 respectively) which have been registered in France by Merck B.V. since 2002. In addition, reference is made to the Glucovance authorisation in Germany (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference products Glucovance 500 mg/2.5 mg and 500 mg/5 mg film-coated tablets, registered in France. A bioequivalence study is the widely accepted means of
demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as this is not required for generic medicinal products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substances
The drug product, Metformine HCl/Glibenclamide Sandoz 500 mg/2.5 mg and 500 mg/5 mg film-coated tablets, which are used in the treatment of diabetes, contain 2 active substances: metformin hydrochloride and glibenclamide. The substances are discussed separately.

Metformin hydrochloride
Metformin hydrochloride is an established active substance which is described in the European Pharmacopoeia (Ph. Eur.*). The active substance is highly soluble in water. Metformin hydrochloride is manufactured as polymorphic form A. For the drug substance a CEP has been provided.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Manufacture
The manufacturing process is covered by the CEP.

Quality control of drug substance
The drug substance specification is in line with the CEP, with additional requirements for residual solvents. The specification is acceptable in view of the Ph.Eur. monograph. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 2 full-scale batches from both drug substance manufacturers.

Stability of drug substance
Stability data on the active substance from one manufacturer have been provided for 3 full scale batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months). The batches were adequately stored. No changes are seen at both conditions. The proposed retest period of 2 years without additional storage conditions is acceptable.

The active substance from the other manufacturer, is stable for 1 year when adequately stored. Assessment thereof was part of granting the CEP and has been granted by the EDQM.
Glibenclamide
Glibenclamide is an established active substance which is described in the European Pharmacopoeia. The active substance is practically insoluble in water. Glibenclamide does not exhibit polymorphism or chirality.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
Two starting materials are used. The manufacturing process consists of 4 reaction steps. Methanol is used as a solvent in the final step. No class 1 organic solvents or heavy metal catalysts are used.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for 11 full-scale batches stored at 25°C/60% RH (12 – 60 months) and on three full-scale batches stored at 40°C/75% RH (6 months). The batches were adequately stored. No changes are observed at both storage conditions. The proposed retest period of 5 years without special storage conditions is acceptable.

* Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Medicinal Product

Composition
Metformine HCl/Glibenclamide Sandoz 500 mg/2.5 contains 500 mg metformin hydrochloride, equivalent to 390 mg metformin, and 2.5 mg glibenclamide, and is an almost white, oval biconvex film-coated tablet. Metformine HCl/Glibenclamide Sandoz 500 mg/5 mg contains 500 mg metformin hydrochloride, equivalent to 390 mg metformin, and 5 mg glibenclamide, and is a dark pink, oval biconvex film-coated tablet.

The film-coated tablets are packed in Al/Al blister packs.

The excipients are:

**Tablet core:** microcrystalline cellulose (E460), povidone (E1201), croscarmellose sodium (E468), and magnesium stearate (E572).

**Tablet coating:** hypromellose (E464), hydroxypropyl cellulose (E463), macrogol, titanium dioxide (E171), Iron oxide brown (E172), and talc (E553b).

The excipients and packaging are usual for this type of dosage form.

The composition of the tablets is the same except that the amount of cellulose in the tablet formulation 500mg/5mg is proportional lower to compensate for the increase of glibenclamide content.
Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Development studies have been performed in order to optimize the composition of the tablet core and the manufacturing process. The choices of the packaging and manufacturing process are justified. The composition of the batches used in the clinical studies is manufactured according to the finalized process and composition. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The main steps of the manufacturing process are wet granulation, tablet compression and coating. Because of the relatively low content of glibenclamide and in order to assure content uniformity, first a granulate (A) is prepared from the glibenclamide drug substance with part of the metformin hydrochloride and tablet core excipients. A second granulate (B) is then prepared from the remaining metformin hydrochloride and excipients. These separate granulates are then blended together and compressed into tablets. Because of the low content of glibenclamide, the manufacturing process is considered non-standard. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 4 full-scale batches per tablet strength.

Excipients
Except for iron oxide, the excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification, water content, assay, uniformity of dosage units, related substances, dissolution, residual solvents and microbial quality. Except for assay, water content and related substances of glibenclamide, the release and shelf-life requirements are identical. The specifications are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 4 full-scale batches per strength, demonstrating compliance with the release specification.

Stability tests on the finished product
Stability data on the product has been provided 4 full-scale batches per tablet strength, stored at 25°C/60% RH (9-12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Al/Al-blisters. No significant changes are observed at both conditions. The proposed shelf life of 2 years for the product without any special storage requirement is justified.
The MAH has committed to continue the stability studies at least throughout the proposed shelf-life of 24 months according to the stability protocol.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects
This product is a generic formulation of Glucovance, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of metformin or glibenclamide released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.
II.3 Clinical aspects

Metformin and glibenclamide are a well-known active substances with established efficacy and tolerability.

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test products Metformine HCl/Glibenclamide Sandoz 500 mg/2.5 mg and 500 mg/5 mg film-coated tablets (Sandoz B.V., the Netherlands), are compared with the pharmacokinetic profile of the reference products Glucovance 500 mg/2.5 mg and 500 mg/5 mg film-coated tablets (Merck B.V., France).

The choice of the reference product

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products (if applicable) in different member states.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study 1 – 500 mg/2.5 mg

A single-dose, randomised, two-way, crossover bioequivalence study was carried out under fed conditions in 46 healthy male volunteers. Following an overnight fast of at least 10 hours, subjects received a high-fat, high-calorie breakfast 30 minutes prior to drug administration. The breakfast consisted of 240 mL of whole milk, 2 eggs fried in butter, 4 ounces of hash brown potatoes (2 potato patties), 1 English muffin with 11 g of butter and 2 strips of bacon. Thirty minutes after the start of the breakfast, a single dose (500 mg/2.5 mg) of the assigned formulation was administered orally with 240 mL of water at ambient temperature, starting at 08:30, to one subject per minute. Approximately 60 mL of grape juice was subsequently administered about 1, 2 and 3 hours after dosing to minimize the hypoglycemic effects of metformin/glibenclamide. Meals were provided no less than 4 hours after drug administration. Water was allowed ad libitum until 2 hours pre-dose and 2 hours after drug administration. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 12, 16, 24 and 30 hours after administration of the products.

The analytical method is adequate validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Forty-three subjects completed the study. Two subjects were withdrawn because of positive drug test before dosing of period 2. A third subject was withdrawn by the study investigator prior to dosing in period 2 because for safety reasons (many episodes of diarrhoea). Though plasma samples were analyzed for all 43 subjects the data of these three subjects were not included in the statistical analyses. Forty subjects were therefore included in the final analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean [%CV], t\textsubscript{max} (mean, [%CV]) of metformine under fed conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=40</th>
<th>AUC\textsubscript{0-1} ng.h/ml</th>
<th>AUC\textsubscript{0-∞} ng.h/ml</th>
<th>C\textsubscript{max} ng/ml</th>
<th>t\textsubscript{max} h</th>
<th>t\textsubscript{1/2} h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td></td>
<td>3.94 [28.0]</td>
<td>4.15 [27.3]</td>
<td>571.6 [29.5]</td>
<td>3.50 [41.3]</td>
<td>3.14 [18.6]</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td></td>
<td>96.3 (92.9 – 99.8)</td>
<td>96.6 (93.4 – 1.00)</td>
<td>93.67 (89.7 – 97.8)</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>
Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean [%CV], \( t_{\text{max}} \) (mean [%CV]) of glibenclamide under fed conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( \text{AUC}<em>{0-t} ) ( \text{AUC}</em>{0-\infty} )</th>
<th>( C_{\text{max}} )</th>
<th>( t_{\text{max}} )</th>
<th>( t_{1/2} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>520.47 [36.7]</td>
<td>539.56 [36.1]</td>
<td>107.71 [28.3]</td>
<td>2.5 [52.9]</td>
</tr>
<tr>
<td>Reference</td>
<td>520.18 [36.7]</td>
<td>538.54 [35.2]</td>
<td>104.47 [31.7]</td>
<td>2.00 [52.3]</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>99.8 (96.5 – 103.2)</td>
<td>99.7 (96.6 – 103.0)</td>
<td>104.73 (95.8 – 114.5)</td>
<td>---</td>
</tr>
<tr>
<td>CV (%)</td>
<td>9.3</td>
<td>8.8</td>
<td>24.9</td>
<td>---</td>
</tr>
</tbody>
</table>

*In-transformed values

The 90% confidence intervals calculated for \( \text{AUC}_{0-t} \), \( \text{AUC}_{0-\infty} \) and \( C_{\text{max}} \) of both active ingredients are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of both metformin and glibenclamide under fed conditions, it can be concluded that Metformine HCl/Glibenclamide Sandoz 500 mg/2.5 mg film-coated tablets and Glucovance 500 mg/2.5 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

**Bioequivalence study 2 – 500 mg/5 mg**

A single-dose, randomised, two-way, crossover bioequivalence study was carried out under fed conditions in 44 healthy male volunteers. Following an overnight fast of at least 10 hours, subjects received a high-fat, high-calorie breakfast 30 minutes prior to drug administration. The breakfast consisted of 240 mL of whole milk, 2 eggs fried in butter, 4 ounces of hash brown potatoes (2 potato patties), 1 English muffin with 11 g of butter and 2 strips of bacon. Thirty minutes after the start of the breakfast, a single dose (500 mg/5 mg) of the assigned formulation was administered orally with 240 mL of water at ambient temperature, starting at 08:30, to one subject per minute. Approximately 60 mL of grape juice was subsequently administered about 1, 2 and 3 hours after dosing to minimize the hypoglycemic effects of metformin/glibenclamide. Meals were provided no less than 4 hours after drug administration. Water was allowed ad libitum until 2 hours pre-dose and 2 hours after drug administration. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 12, 16, 24 and 30 hours after administration of the products.
The analytical method is adequate validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Forty-two subjects completed the study. Six subjects were withdrawn from the study, prior to plasma analysis, due to diarrhoeal episodes post-dosing that may affect drug absorption. Two subjects withdrew for personal reasons after the first period and before a second dose was administered. Though plasma samples were analyzed for all 44 subjects the data of these eight subjects were not included in the statistical analyses. Thirty-six subjects were therefore included in the final analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean [%CV], t\textsubscript{max} (mean [%CV]) of metformine under fed conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=36</th>
<th>AUC\textsubscript{0-t} (ng.h/ml)</th>
<th>AUC\textsubscript{0-∞} (ng.h/ml)</th>
<th>C\textsubscript{max} (ng/ml)</th>
<th>t\textsubscript{max} (h)</th>
<th>t\textsubscript{1/2} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Ratio (90% CI)</td>
<td>99.9 (96.3 – 103.7)</td>
<td>99.8 (96.2 – 103.5)</td>
<td>99.7 (96.0 – 103.4)</td>
<td>---</td>
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<td></td>
</tr>
<tr>
<td>CV (%)</td>
<td>9.3</td>
<td>9.2</td>
<td>9.3</td>
<td>---</td>
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</tr>
</tbody>
</table>

AUC\textsubscript{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC\textsubscript{0-∞} area under the plasma concentration-time curve from time zero to infinity
C\textsubscript{max} maximum plasma concentration
t\textsubscript{max} time for maximum concentration
t\textsubscript{1/2} half-life

*In-transformed values

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean [%CV], t\textsubscript{max} (mean [%CV]) of glibenclamide under fed conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=36</th>
<th>AUC\textsubscript{0-t} (ng.h/ml)</th>
<th>AUC\textsubscript{0-∞} (ng.h/ml)</th>
<th>C\textsubscript{max} (ng/ml)</th>
<th>t\textsubscript{max} (h)</th>
<th>t\textsubscript{1/2} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>1042.9 [31.5]</td>
<td>1074.0 [31.2]</td>
<td>253.0 [33.1]</td>
<td>2.50 [49.9]</td>
<td>3.79 [34.0]</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>1016.9 [30.0]</td>
<td>1046.1 [30.1]</td>
<td>229.6 [30.1]</td>
<td>2.5 [43.4]</td>
<td>4.44 [47.7]</td>
<td></td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>102.5 (99.6 – 105.4)</td>
<td>102.7 (100.0 – 105.6)</td>
<td>109.5 (100.8 – 119.0)</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>CV (%)</td>
<td>7.0</td>
<td>6.8</td>
<td>21.1</td>
<td>---</td>
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</tr>
</tbody>
</table>

AUC\textsubscript{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC\textsubscript{0-∞} area under the plasma concentration-time curve from time zero to infinity
C\textsubscript{max} maximum plasma concentration
t\textsubscript{max} time for maximum concentration
t\textsubscript{1/2} half-life

*In-transformed values
The 90% confidence intervals calculated for $\text{AUC}_{0-t}$, $\text{AUC}_{0-\infty}$ and $C_{\text{max}}$ of both active ingredients are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of both metformin and glibenclamide under fed conditions, it can be concluded that Metformine HCl/Glibenclamide Sandoz 500 mg/5 mg film-coated tablets and Glucovance 500 mg/5 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

**Risk management plan**

There is more than 10 years post-authorisation experience with both active substances. The safety profile of metformin and glibenclamide can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

**Product information**

**SPC**

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Glucovance marketed by Merck B.V.

**Readability test**

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.

The test consisted of a pilot test followed by two rounds with 10 participants each. The readability test itself and the evaluation report are of an acceptable quality. There were sufficient questions about the critical sections. The conclusions are clear, concise and clearly presented. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Metformine HCl/Glibenclamide Sandoz 500 mg/2.5 mg and 500 mg/5 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Glucovance 500 mg/2.5 mg and 500 mg/5 mg film-coated tablets. Glucovance is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Metformine HCl/Glibenclamide Sandoz 500 mg/2.5 mg and 500 mg/5 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 19 October 2009. Metformine HCl/Glibenclamide Sandoz is authorised in the Netherlands on 16 November 2009.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from 19 October 2009 to 18 October 2012.

The date for the first renewal will be: June 2013.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product
- The MAH has committed to continue the stability studies at least throughout the proposed shelf-life of 24 months according to the stability protocol.
### List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification</td>
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<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
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<tr>
<td>BP</td>
<td>British Pharmacopoeia</td>
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<tr>
<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximum plasma concentration</td>
</tr>
<tr>
<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
</tr>
<tr>
<td>EDMF</td>
<td>European Drug Master File</td>
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<tr>
<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<td>GCP</td>
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<td>GMP</td>
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<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<td>Marketing Authorisation Holder</td>
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<tr>
<td>MEB</td>
<td>Medicines Evaluation Board in the Netherlands</td>
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<tr>
<td>OTC</td>
<td>Over The Counter (to be supplied without prescription)</td>
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<tr>
<td>PAR</td>
<td>Public Assessment Report</td>
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<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PIL</td>
<td>Package Leaflet</td>
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<td>PSUR</td>
<td>Periodic Safety Update Report</td>
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<td>SD</td>
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<td>SPC</td>
<td>Summary of Product Characteristics</td>
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<td>t&lt;sub&gt;½&lt;/sub&gt;</td>
<td>Half-life</td>
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<td>t&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Time for maximum concentration</td>
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<td>USP</td>
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### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
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