CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Metformine HCl Sandoz 500 mg and 850 mg, film-coated tablets Sandoz BV, the Netherlands

metformin

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.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1171/001-002/DC
Registration number in the Netherlands: RVG 100935, 100936

Date of firt authorisation: 10 February 2009
Last revision: 21 December 2010

Pharmacotherapeutic group:	Blood glucose lowering drugs, excl. insulins; biguanides
ATC code:	A10BA02
Route of administration:	oral use
Therapeutic indication:	type 2 diabetes mellitus
Prescription status:	prescription only
Date of authorisation in NL:	5 February 2009.
Concerned Member States:	Decentralised procedure with IE and IT
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 500 mg and 850 mg, film-coated tablets from Sandoz B.V. The date of authorisation was on 5 February 2009 in the Netherlands. The product is indicated for treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.

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

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.
Controlled clinical studies in a limited paediatric population aged 10-16 years with type 2 diabetes treated during one year demonstrated a similar response in glycaemic control to that seen in adults.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Glucophage which has been registered in Finland by Lipha S.A. Merck, France since 1967 (original product). In addition, reference is made to Glucophage® authorisations in the individual member states (reference product, NL License RVG 00447).

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 products is compared with the pharmacokinetic profile of the reference products Glucophage® 500 and 850 mg, registered in Germany. 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. These generic products can be used instead of their 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.

No paediatric development programme needs to be submitted for this generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

Active substance

General information
The active substance is metformine hydrochloride and is described in the European Pharmacopoeia (Ph.Eur.).

The CEP procedure is used for the different active substance manufacturers. 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 suitablity 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.

Manufacturing process
This is covered by the CEP.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. and with the CEP, with additional requirements for other impurities. The specification is acceptable in view of the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided and/or are in compliance with the specifications is part of the CEP.

Stability of drug substance
Stability data on three batches of the active substance have been provided for one of the manufacturers. The batches were stored at 25°C/60% RH for 66 months and at 40°C/75% RH for 6 months. The batches were adequately stored. No increase or decrease for any of the tested parameters is observed. The claimed re-test period of 5 years without specific storage condition, when stored under the proposed conditions.

The active substance of the other manufacturers is stable for respectively 5 years and 1 year, when stored in PE plastic bag in paper drum or paper carton and stored under the proposed conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** 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.*

Drug Product

Composition
The drug products are white, film-coated tablets with break line on both sides. Two different strengths 500 mg and 850 mg are manufactured. The 500 mg tablets are engraved M500, the 850 mg tablets are engraved M850. The excipients used are: microcrystalline cellulose, sodium starch glycollate (type A), copolyvidone, colloidal anhydrous silica, magnesium stearate, lactose monohydrate,

methylhydroxypropylcellulose, titanium dioxide and macrogol 4000. The tablets are either packed in PP-aluminium blister packs, PVC/PVDC aluminium blister packs or HDPE bottles. The excipients and packagings are usual for this type of dosage form.

Pharmaceutical development

The development of the product has been described. The objective was to develop a product that would be essentially similar to the innovator product Glucophage®. The choice of excipients is justified and their functions explained. The applicant's objective was to obtain a formulation of film-coated tablets containing metformin hydrochloride which is similar to the innovator's product. In the course of formulation development the granulation process was changed from organic to aqueous in order to minimize environmental pollution.
Dissolution profiles of prototype products manufactured with the organic granulation fluid and the innovator's product versus the proposed products manufactured with the aqueous granulation fluid are compared and meet the BP requirements of not less than 75% (Q) after 30 minutes.
The influence of hardness of the tablets on dissolution was examined, no difference was found. Divisibility was checked and complied with the Ph.Eur. requirements.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process

Granules of metformine hydrochloride are made by aqueous granulation. The granules are mixed and sieved with other excipients to form the tabletting mass of which the cores are pressed. Then the cores are coated. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the 500 mg product have been presented for nine full-scaled batches. On the 850 mg product process validation data have been presented for 24 full scale batches.

Excipients

All the individual excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product

The drug product specification includes tests for appearance, identity, assay, degradation, uniformity of dosage units, resistance to crushing, disintegration, dissolution and microbiology.
The release and shelf-life specifications are identical and are acceptable.
It has been demonstrated that the applied method for impurity testing and for determining the assay is capable of detecting all potential degradation products of metformin (stability indicating).
All analytical methods have been adequately described and validated.
Batch analytical data from the proposed production from both production sites have been provided on nine full scale batches of the 500 mg strength and 24 full scale batches of the 850 mg product, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the 500 mg and 850 mg product have been provided on respectively 19 and 21 full - scaled and pilot-scaled batches. The batches were stored at 25°C/60% RH up to 60 months and 40°C/75% RH up to 6 months. Some batches were stored at 30°/65% RH up to 12 months. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in BOTH blister packs and HDPE bottles
Since all parameters stay within the shelf life limits during normal and accelerated testing and no up or down trends are observed a shelf-life of 60 months seems acceptable. A photostability study performed on the tablets packed in the HDPE bottles demonstrated a slight coloration therefore the indication store in the bottle in the outer carton in order to protect from light is added to the HDPE bottles. The granted shelf life is 60 months in PVC/PVDC-aluminium blisters or PP-blisters without storage conditions or 60 months in HDPE bottles with the indication store in the original package to protect from light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

A Certificate of suitability for lactose monohydrate, issued by the EMEA, has been provided and compliance with the Note for Guidance, on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products, has been satisfactorily demonstrated.

For Magnesium stearate a statement claiming the vegetable origin of magnesium stearate has been included.

II.2 Non clinical aspects

This product is a generic formulation of Glucophage, which is available on the European market for more than 40 years. 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 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 is a well-known active substance with established efficacy and tolerability.

Although the two formulations were dose proportional, the MAH has submitted for this generic formulation two bioequivalence studies in which the pharmacokinetic profile of the test product Metformine HCl Sandoz is compared with the reference product Glucophage, one for the 500 mg strength (Study 2001-57-FTA-1), and one for the 850 mg strength (Study 2001-58-FTA-1).
The formula and preparation of the bioequivalence batches is identical to the formula proposed for marketing. The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.
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).

Study 2001-57-FTA-1
A single-dose, open, randomized, two-period crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 18-42 years. Each subject received a single dose (500 mg) of one of the 2 metformin formulations. The tablet was orally administered with 240 ml water. No food was allowed from 12 hours before dosing until at least 4 hours after dosing.
Blood samples were collected prior to study drug administration and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12 and 14 hours post-dose.
The analytical method is adequately 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
Twenty-eight subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters for metformin (as arithmetic mean ± SD, t_{max} as median (range)) under fasted conditions.

Treatment N=28	**AUC_{0-t}** µg/ml/h	**$AUC_{0-\infty}$** µg/ml/h	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	7.15 ± 1.70	7.52 ± 1.80	1.21 ± 0.35	3.0 (0.5-4.5)	2.8 ± 0.4
Reference	7.93 ± 2.37	8.32 ± 2.49	1.29 ± 0.38	3.0 (0.5-5.0)	2.9 ± 0.4
***Ratio (90% CI)**	0.91 (0.84-0.99)	0.91 (0.85-0.98)	0.94 (0.85-1.03)	0.02 (-0.33-0.37)	---
CV (%)	17.1	16.7	19.3	---	---

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} 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 metformin under fasted conditions, it can be concluded that Metformine HCl Sandoz 500 mg and Glucophage 500 mg are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Study 2001-58-FTA-1

A single-dose, open, randomized two-period crossover bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 18-40 years. Each subject received a single dose (850 mg) of one of the 2 metformin formulations. The tablet was orally administered with 240 ml water. No food was allowed from 12 hours before dosing until at least 4 hours after dosing.

Blood samples were collected prior to study drug administration and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12 and 14 hours post-dose.

The analytical method is adequately 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

Twenty-four subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters for metformin (as arithmetic mean ± SD, t_{max} as median (range)) under fasted conditions.

Treatment N=24	**AUC_{0-t}** µg/ml/h	**$AUC_{0-\infty}$** µg/ml/h	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	9.83 ± 2.41	10.32 ± 2.55	1.67 ± 0.37	3.0 (1.5-4.0)	2.9 ± 0.4
Reference	9.05 ± 2.37	9.52 ± 2.47	1.63 ± 0.44	2.5 (1.0-4.0)	3.0 ± 0.4
***Ratio (90% CI)**	1.09 (1.00-1.19)	1.09 (1.00-1.19)	1.03 (0.95-1.12)	0.25 (0.00-0.50)	---
CV (%)	17.9	17.7	17.6	---	---

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} 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 metformin under fasted conditions, it can be concluded that Metformin HCl Sandoz 850 mg and Glucophage 850 mg are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

In conclusion: Bioequivalence of the Metformin HCl Sandoz 500 mg and Glucophage 500 mg, as well as between Metformin HCl Sandoz 850 mg and Glucophage 850 mg reference tablets was adequately shown using appropriate bioequivalence studies.

Risk Management Plan and Pharmacovigilance system
Metformin was first approved in 1967, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of metformin 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
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Glucophage marketed by Merck. For the package leaflet the text of Glucophage was also used as reference.

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 two rounds with 10 participants in the first round and 12 participants in the second round. A written readablity test procedure was used performed via a questionnaire with 15 open questions on the content of the leaflet and 17 statements regarding the package leaflet structure. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. There were sufficient questions about the critical sections. The results were satisfactory, i.e. in the first round the participants located and understood 94.6% of the information queried in each question concerning the content of the final package leaflet. In the second round this percentage was 93.6%. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Metformine HCl Sandoz 500 mg and 850 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Glucophage. Glucophage 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 and are in agreement with other metformin containing products. Braille conditions are met by the MAH.

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 member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Metformine HCl Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 14 October 2008. Metformine HCl Sandoz is authorised in the Netherlands on February 5th, 2009.

Metformin takes part in the PSUR synchronisation project of the Heads of Medicines Agencies. In view of the EU work sharing project, the MAH will follow the harmonised birth date and it's data lock point. The allocated first data lock point for metformin is April 2009. The first PSUR is expected within 60 days from data lock point. Thereafter the PSUR submission cyclus is 3 years.

The date for the first renewal will be December 2012

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Submission of a new or updated Ph. Eur. Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance. From a manufacturer currently approved.	NL/H/1171/ 001-002/IA/ 001	IA	22-10-2009	5-10-2009	Approval	N
Change in test procedure of the finished product. Other changes to a test procedure, including replacement or addition of a test procedure.	NL/H/1171/ 001-002/IB/ 002	IB	6-10-2009	5-11-2009	Approval	N
Change in batch size of the active substance or intermediate. Up to 10-fold compared to the original batch size approved at the grant of the marketing authorisation.	NL/H/1171/ 001-002/IA/ 003	IA	12-1-2010	26-1-2010	Approval	N
B.II.a, unforeseen. The Opdary coating film is replaced by a lactose free coating film.	NL/H/1171/ 001-002/IB/ 004	IB	27-8-2010	26-9-2010	Approval	N
Deletion of manufacturing sites (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier). Deletion of Dragenopharm Apotheker, Germany	NL/H/1171/ 002/IA/ 005	IA	8-7-2010	7-8-2010	Approval	N
Submission of a new or updated Ph. Eur. certificate of suitability: For an active substance For a starting material/reagent/intermediate used in the manufacturing process of the active substance For an excipient B.III.1.a) European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. 3 New certificate from a new manufacturer (replacement or addition).	NL/H/1171/ 001-002/IA/ 006	IA	10-9-2010	11-10-2010	Approval	N