CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Metformine HCl Vale 500 mg, 850 mg, and 1000 mg film-coated tablets
Vale Pharmaceuticals Ltd., Ireland

metformin (as hydrochloride)

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/1570/001-003/MR
Registration number in the Netherlands: RVG 103638,103639,103640

1 March 2010

Pharmacotherapeutic group:	blood glucose lowering drugs, excl. insulins; biguanides
ATC code:	A10BA02
Route of administration:	oral
Therapeutic indication:	type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycemic control. In adults, Meformin HCl Vale film-coated tablets may be used as monotherapy or in combination with other oral anti-diabetic agents or with insulin. In children from 10 years of age and adolescents, Metformin HCl Vale film-coated tablets may be used as monotherapy or in combination with insulin.
Prescription status:	prescription only
Date of authorisation in NL:	13 January 2010
Concerned Member States:	Mutual recognition procedure with AT, BE, BG, CZ, DE, DK, ES, FI, FR, HU, IE, NO, PL, PT, RO, SE, SK, and UK
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 Vale 500 mg, 850 mg, and 1000 mg film-coated tablets, from Vale Pharmaceuticals Ltd. The date of authorisation was on 13 January 2010 in the Netherlands. The product is indicated for:

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 glycemic control.

In adults – Meformin HCl film-coated tablets may be used as monotherapy or in combination with other oral anti-diabetic agents or with insulin.

In children - from 10 years of age and adolescents, Metformin HCl film-coated tablets may be used as monotherapy or in combination with insulin.

A reduction of diabetic complications has been shown in overweight type 2 diabetic adult patients treated with metformin hydrochloride as first-line therapy after diet failure.

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

Metformin hydrochloride 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 hydrochloride 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 utilization
- and delay of intestinal glucose absorption.

Metformin hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin hydrochloride increases the transport capacity of all types of membrane glucose transporters (GLUTs) known to date.
In humans, independently of its action on glycaemia, metformin hydrochloride has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin hydrochloride reduces total cholesterol, LDL cholesterol and triglyceride levels.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Glucophage 500 mg and 850 mg film-coated tablets, both registered in the UK, and Glucophage 1000 mg film-coated tablets, registered in Germany. In the Netherlands Glucophage 500 (RVG 00447) is registered since 24 October 1967, Glucophage 850 (RVG 05934) since 15 July 1970, and Glucophage 1000 (RVG 26510) since 18 June 2001, all with Merck BV, NL as the registration holder. These products were withdrawn from the Netherlands on 31 December 2008 for commercial reasons.

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 Glucophage 500 mg and 1000 mg 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 substance
The active substance is metformin hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is freely soluble in water. 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 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.

Manufacture
The manufacturing process is covered by the CEP.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur., with additional requirements for residual solvents and the limit for unidentified impurities. The specification is acceptable in view of the CEP. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 full scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for 6 full scaled batches stored at 30°/65% RH (3 batches for 12 and 3 batches for 36 months) and 40°/75% RH (6 months). The batches were adequately stored. No changes were seen at both conditions. The proposed retest period of 4 years without any additional storage requirements is justified.

** 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
Metformin film-coated tablets are available in 3 strengths containing 500 mg, 850 mg or 1000mg metformin hydrochloride. The tablet core consists further of magnesium stearate and povidone K-30. The tablet coating consists of hypromellose, hydroxypropylcellulose and macrogol 400 and 8000. The 500 mg tablets have break line to facilitate swallowing and the 1000 mg tablets have a break line for equal division in two halves. For the 1000 mg tablets uniformity of mass of subdivided tablets was tested in 3 batches of 1000 mg showing compliance with the Ph.Eur. acceptance criteria. The drug product is packed in clear transparent PVC/Al-blisters or white opaque HDPE bottles. The excipients and packaging are usual for this type of dosage form.
The different strengths of the drug product are manufactured fully dose-proportionally.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed regarded the formulation development, development of the dissolution method and the performance of comparative dissolution studies with the originator product (Glucophage). The choices of the packaging materials and the manufacturing process are justified. The batches used for the BE studies have the same composition as the final drug product. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The main steps of the manufacturing process are compounding, granulation, drying, tablet compression and film-coating. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 3 pilot-scale batches. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post-authorization.

Excipients
The excipients comply with Ph.Eur. or in-house criteria. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification, dissolution, uniformity of dosage units, related substances, assay, water content, microbial limits and uniformity of mass for the subdivided tablets (500 and 1000 mg tablets). The release and shelf-life limits 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 3 pilot scale batches per strength, demonstrating compliance with the release specifications.

Stability tests of the finished product
Stability data on the product has been provided for 3 pilot scale batches per strength of the drug product manufactured at the proposed manufacturing site, stored at 25°C/60% RH (9 months) and 40°C/75% RH (6 months). However, based on additional stability data from the same drug product manufactured at an Australian site are accepted as supportive. These stability data are provided on 6 full-scale batches of 500 mg and 850 mg tablets stored at 25°C/60% RH or 30°C/60% RH (up to 36 months) and at 40°C/75% RH (6 months) and 3 full-scale batches of 1000 mg tablets stored at 30°C/65% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline (or tighter). The batches were stored in PVC/Al-blisters or HDPE bottles. No changes were seen under all storage conditions. The proposed shelf life of 36 months for the PVC/Al-blisters and 24 months for the HDPE bottle are justified.
The MAH has committed to continue to test the batches currently undergoing stability up to 60 months at long term conditions in the HDPE bottle and blister pack.

In-use stability
The MAH has committed to perform in-use stability on exhibit batches of metformin tablets in HDPE pack, on first commercial lot of metformin tablets 500mg (HDPE bottle) 30-count, patient pack as per the in-use 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 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.

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test product Metformine HCL Vale 500 mg and 1000 mg film-coated tablets (Vale Pharmaceuticals Ltd., Ireland) are compared with the pharmacokinetic profile of the reference products Glucophage 500 mg and 1000 mg tablets (Merck Santé, 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 tablets
An open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose, comparative relative bioavailability study was carried out under fed conditions in 30 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 within 30 min of a high fat, high caloric breakfast. There were 2 dosing periods, separated by a washout period of 7 days.
Blood samples were collected predose and at 0.5, 1.0, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.25, 3.5, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 24.0 and 36.0 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.

In the SPC it is stated that metformin should be given during or after meals. In this respect a bioequivalence study under fed conditions is acceptable. No fasting study is required given that metformin is not well tolerated under fasting conditions

Results
Twenty-eight of the 30 volunteers were dosed in a randomised matter. Twenty six volunteers completed both study periods. One subject was withdrawn by the clinical investigator as he vomited during the first period and one subject did not show up in the second period.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of metformin under fed conditions.

Treatment N=26	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	6806 ± 1180	6910 ± 1185	781 ± 184	4.0 (1.0 – 6.0)	3.7 ± 0.4
Reference	6628 ± 1191	6760 ± 1157	741 ± 151	4.5 (1.75 – 6.0)	3.7 ± 0.4
***Ratio (90% CI)**	1.03 0.99 – 1.07	1.02 0.98 – 1.06	1.05 1.01 – 1.09	---	---
CV (%)	8.6%	7.9%	8.5%	---	---

$AUC_{0-\infty}$ 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 fed conditions, it can be concluded that Metformine HCl Vale 500 mg and the Glucophage 500 mg 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 – 1000 mg tablets
An open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose, comparative relative bioavailability study was carried out under fed conditions in 30 healthy male subjects, aged 20-41 years. Each subject received a single dose (1000 mg) of one of the 2 metformin formulations. The tablet was orally administered within 30 min of a high fat, high caloric breakfast. There were 2 dosing periods, separated by a washout period of 7 days.
Blood samples were collected predose and at 0.5, 1.0, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.25, 3.5, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 24.0 and 36.0 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
Twenty-eight of the 30 volunteers were dosed in a randomised matter. All twenty-eight volunteers completed both study periods.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of metformin under fed conditions.

Treatment N=28	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	12.6 ± 2.75	12.8 ± 2.76	1.35 ± 0.27	4.5 (1.8 – 7.0)	4.12 ± 0.55
Reference	12.1 ± 2.62	12.3 ± 2.58	1.31 ± 0.25	5.0 (1.75 – 6.0)	4.05 ± 0.63
***Ratio (90% CI)**	1.04 0.99 – 1.10	1.04 1.00 – 1.09	1.03 0.97 – 1.10	---	---
CV (%)	10%	11%	13%	---	---

$AUC_{0-\infty}$ 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 fed conditions, it can be concluded that Metformine HCl Vale 1000 mg and the Glucophage 1000 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation of results
The conditions for waiving of a study with the 850 mg tablets have been met. The tablets are all dose proportional, the pharmacokinetics of the active substance show linear pharmacokinetics, and the tablets have been manufactured by the same manufacturer and the same manufacturing process. The results of the bioequivalence study performed with the 500 mg and 1000 mg film-coated tablets therefore also apply to the 850 mg strengths.

The MEB has been assured that the bioequivalence study has 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 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

SPC
The content of the SPC approved during the mutual recognition procedure is in accordance with the SPC harmonised via a referral to the CPMP under Article 11 of Council Directive 75/319, as amended. A decision was issued in February 2001.

Readability test
The MAH to the readability test performed with the package leaflet for the product "Metformin Hydrochloride 500 mg/5 ml oral solution". This product belongs to the same class of medicinal products and has the same route of administration as the Metformine HCl Vale tablets.

The MAH submitted a justification which critically appraises the similarities/differences between the submitted PL for Metformine HCl Vale film-coated tablets and the tested PL, and addressed the relevance of test results with the reference PL. In addition, a critical comparison of the design and layout of both PLs was also included. The bridging study report which describes the comparison of both package leaflets, focussed on the areas of the target population, the key safety messages, the design and lay-out issues and the content issues:
-the target population of both package leaflets.
-concerning the bridging report with regard to the key safety messages of both package leaflets, the MAH included a table which outlines the questions used in the user test and how these questions cover key safety messages in both package leaflets. Only two questions of the user test were not applicable as a result of the different excipients in both products and as a result of a different dosage form.
-the layout of the information included in both package leaflets is different as they are made by two different companies. However, at least 5 approvals were received by the MAH of its "in-house" style and therefore the layout is considered acceptable.
-the content of both package leaflets has been compared in a table which clearly shows the differences in content and layout of the two PLs and comments on the readability of the PL for Metformine HCl Vale film-coated tablets. The messages and language used in the two PLs are very similar.

Taken together, the absence of test results from consultation with target patient groups for Metformine HCl Vale film-coated tablets is justified by referring to the tested package leaflet of "Metformin Hydrochloride 500mg/5 ml oral solution". The key messages for safe use have been adequately addressed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Metformine HCl Vale 500 mg, 850 mg, and 1000 mg film-coated tablets have a proven chemical-pharmaceutical quality and are a generic form of Glucophage tablets. 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. 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 Vale 500 mg, 850 mg, and 1000 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 29 November 2009. Metformine HCl Vale is authorised in the Netherlands on 13 January 2010.

A European harmonised birth date has been allocated (19 March 1959) and subsequently the first data lock point is April 2012. The first PSUR will cover the period from November 2009 to April 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 31 December 2012.

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

Medicinal product

- The MAH has committed to continue to test the batches currently undergoing stability up to 60 months at long term conditions in the HDPE bottle and blister pack.
- The MAH has committed to perform in-use stability on exhibit batches of metformin tablets in HDPE pack, on first commercial lot of metformin tablets 500mg (HDPE bottle) 30-count, patient pack as per the in-use stability protocol.
- The MAH has committed to perform process validation for full scaled batches post-authorization.

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
PIL	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