

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

Metformine HCl Aurobindo 500 mg, 850 mg, and 1000 mg film-coated tablets

Aurobindo Pharma Limited, UK

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/1459/001-003/MR

Registration number in the Netherlands: RVG 31685, 31686, 31687

25 May 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. <i>In adults</i> , Meformin HCl Aurobindo film-coated tablets may be used as monotherapy or in combination with other oral anti-diabetic agents or with insulin. <i>In children from 10 years of age</i> and adolescents, Metformin HCl Aurobindo film-coated tablets may be used as monotherapy or in combination with insulin.
Prescription status:	prescription only
Date of first authorisation in NL:	27 April 2006
Concerned Member States:	Mutual recognition procedure with AT, BG, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LV, NO, PL, PT, RO, SE, SI, SK, UK, and BE (only 500 mg and 1000 mg)
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 Aurobindo 500 mg, 850 mg, and 1000 mg film-coated tablets, from Aurobindo Pharma Limited. The date of authorisation was on 27 April 2006 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.

In adults - Metformin HCl Aurobindo 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 Aurobindo 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 three bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference products Glucophage 500 mg and 850 mg tablets, registered in the UK, and Glucophage 1000 mg tablets, 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. 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. The CEP procedure is used for the 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 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 specifications from the Ph. Eur. monograph on metformin hydrochloride are applicable plus additional requirements from the CEPs. The specifications as applied by the drug product manufacturers are considered to be adequate.

Stability of drug substance

For the drug substance from the first manufacturer, a re-test period of 2 years is applicable in view of the re-test period stated on R0-CEP 2004-088-Rev 02, when adequately stored.

For the drug substance from the second manufacturer, a re-test period of 5 years is applicable without specific temperature, when adequately stored.

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

Medicinal Product

Composition

The products are formulated as film-coated tablets and are packaged in PVC / PVDC/Al blister packs. Three strengths are developed: Metformine HCl Aurobindo 500 mg, 850 mg, and 1000 mg, containing 390 mg, 663 mg, and 780 mg of metformin, respectively.

Metformin HCl Aurobindo 500 mg: are white, round, biconvex, film-coated tablets with 'A' debossed on one side and '60' debossed on the other side.

Metformin HCl Aurobindo 850 mg: are white, round, biconvex, film-coated tablets with 'A' debossed on one side and '61' debossed on the other side.

Metformin HCl Aurobindo 1000 mg: are white, oval, biconvex, film-coated tablets with 'A' debossed on one side and '62' debossed on the other side. The tablets have a non-functional groove and therefore cannot be broken.

The excipients are:

Tablet core: povidone, magnesium stearate.

Film-coating: hypromellose, macrogol.

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

The 3 tablet formulations are dose proportional.

Pharmaceutical development

The development aim was to develop dose proportional, stable and robust formulations of Metformin tablets in varying strengths of 500, 850 and 1000 mg and to prove that the 850 mg strength was bio-equivalent to the marketed comparator product Glucophage 850 mg tablets, marketed in the UK. For each strength a separate bio-equivalence study has been performed with Glucophage reference products from the UK (500 mg and 850 mg), and from DE (1000 mg). Comparing dissolution results and profiles have been provided for the test- and reference bio-batches used in the bio-equivalence studies mentioned above. Comparing dissolution studies of the proposed product (500-850-1000 mg) have been performed with the corresponding NL originator product and with originator products from AT, BE, DE, DK, ES, FR, IT, PT, and UK, for either the 500 mg or 850 mg strength, the 500 mg + 850 mg strengths, or for all 3 strengths (NL and DE). The dissolution results at 30 minutes are for all products in the range 92.7-101.4 %, and are herewith comparable.

Manufacturing process

The manufacturing steps are described in sufficient detail. The various manufacturing steps comprise sifting (deagglomeration of the drug substance), milling, dry mixing, wet granulation, drying, milling & screening, extra-granular material sifting, blending and compression. A manufacturing flow-chart is present. Manufacturing details like sieve sizes and drying levels (for the granules in a fluid-bed dryer) have been indicated. Concise descriptions of all equipment used in the various manufacturing steps are given.

The MAH provided validation results of 3 pilot-scale batches. Blend uniformity has not been tested considering that the blend is composed of 96.6% drug substance. The common blend has been characterized regarding loss on drying and water content (KF), particle size distribution, untapped and tapped bulk density, and HPLC assay.

The cores are checked regarding appearance, average mass and uniformity of mass, thickness, hardness, friability, and dissolution, on representative samples of the compression process. The coated tablets are checked on appearance, average mass and uniformity of mass, thickness and dissolution, during the coating process. Finally the final coated tablets are tested according to the complete finished product specification. All results were according to the set release specifications. The total number of data (including numerous samples representative for the concerning processing) demonstrates that the manufacturing process is sufficiently under control.

Quality control of drug product

Adequate specifications are applied for the drug product for both release and shelf-life, including a specification for uniformity of dosage units (Ph. Eur. 2.9.40; acceptance value NMT 15) and an adequate specification on Impurity A (1-cyanoguanidine; NMT 0.02%). Also the other Ph. Eur. impurities (B-F) are adequately limited (NMT 0.1%). In view of high maximum daily dosage (3 g, is > 2 g) the specification of any individual unknown impurity NMT 0.10% is correct.

All other specifications are in accordance with or more tight (microbiological purity) than Ph.Eur. specifications or are otherwise not unreasonable. All quantitative analytical methods have been adequately validated.

Breakability

The 1000 mg tablets contain a score-line. The MAH performed the test on breakability on two pilot-scale batches of Metformin 1000 mg tablets, and it showed that the tablets were very difficult to break by hand, similarly as is the case with the NL originator product Glucophage 1000 mg tablets. Because of this difficulty, it is mentioned in the SPC that although the 1000 mg tablets have a score-line, the score at issue is not a functional score, and that the tablets are not breakable. (*"The tablets have a non-functional groove and therefore cannot be broken."*).

Stability tests on the finished product

During stability testing, no significant changes have been observed for one of the test parameters. At six months the microbial purity testing was meeting the requirements during normal and accelerated testing. All results on individual and total impurities are below 0.1%. Up to 36 months there is no change or very slight decrease of assay, and no increase of (total) impurities. Herewith the claimed shelf life of 4 years without specific storage condition can be accepted.

The MAH agreed on various commitments regarding quality aspects, see page 10.

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 metformine 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

Metformine is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted 3 bioequivalence studies in which the pharmacokinetic profile of the test products Metformine HCl Aurobindo 500 mg, 850 mg, and 1000 mg film-coated tablets are compared with the pharmacokinetic profile of the reference products Glucophage 500 mg and 850 mg tablets (Lipha Pharmaceuticals, UK) and Glucophage 1000 mg tablets (Merck, Germany).

The absolute bioavailability of a metformin 500 mg or 850 mg tablet given under fasting conditions is approximately 50-60% because of incomplete absorption. Metformin exhibits less than dose proportional pharmacokinetics in the range 500 to 2250 mg, which is probably due to decreased absorption. Food decreases the extent of (25-40%) and slightly delays the absorption of metformin (increase of 35 minutes in T_{max}). The administration of metformin is advised with food or just after food intake. Plasma elimination half-life is approximately 6 hours. Metformin is excreted unchanged in the urine, ~90 % within the first 24 hours.

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 in different member states.

The formula and preparation of the bioequivalence batches are identical to the formula proposed for marketing.

Bioequivalence study 1 – 500 mg

An open label, randomised, two-treatment, two sequence, two period, cross-over, single dose, comparative bioequivalence study was carried out under fed conditions in 26 healthy male volunteers, aged 18-38 years. Each subject received a single dose (500 mg) of one of the 2 metformine formulations. The tablet was orally administered with 240 ml of 20% glucose solution in water 30 minutes after taking a standardised high-fat, high caloric meal (approx 985 Kcal (60% fat, 25 % carbohydrate and 15% proteins) and was composed of fried eggs (282 Kcal), mutton curry (187 Kcal), bread slices with butter (205 Kcal), fried potatoes (169 Kcal), milk (142 Kcal)). Subjects were given 60 ml of 20% glucose solution in water every 15 minutes for 4 hours after dosing. There were two dosing periods, separated by a washout period of at least 9 days, which is sufficient for a compound with an estimated plasma elimination half-life of 6 hours.

Blood samples were collected predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16 and 24 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

All subjects finished the study. Two adverse events occurred. One concerned the gastrointestinal system (after administration of reference) and was judged to be study related. The other adverse event was a post study laboratory test abnormality, which was judged not to be study related. Pharmacokinetic parameters were evaluated of the first 24 subjects completing the study in a cross-over design which is in accordance with the protocol.

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

Treatment N=24	AUC_{0-t} ng.h/ml	AUC_{0-∞} ng.h/ml	C_{max} ng/ml	t_{max} h	t_{1/2} h
Test	6707 (1817)	6956 (1836.6)	762 (208.8)	4.00 (1.49)	---
Reference	6465 (1695.2)	6694 (1719.8)	713 (206.7)	4.00 (1.69)	---
*Ratio (90% CI)	1.04 (0.96 – 1.11)	1.04 (0.97 – 1.11)	1.07 (0.97 – 1.19)	---	---
CV (%)	14.8	14.2	20.8	---	---

AUC_{0-∞}	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

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} 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 Aurobindo 500 mg film-coated tablets 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 – 850 mg

An open label, randomised, two-treatment, two sequence, two period, cross-over, single dose, comparative bioequivalence study was carried out under fed conditions in 28 healthy male volunteers, aged 18-38 years. After overnight fasting the subjects received an oral dose of 850 mg metformin (1 tablet) of either test or reference formulation with 240 ml of 20% glucose solution in water 30 minutes after taking a standardised high-fat, high caloric meal (2 fried eggs, 1 cup mutton, 3 bread, 2 tsp butter, 1 cup potato curry, 1 glass milk (1000 kcal, 50% fat of total calories)). Subjects were given 60 ml of 20% glucose solution in water every 15 min for 4 hours after dosing. There were two dosing periods, separated by a washout period of at least 7 days, which is sufficient for a compound with an estimated plasma elimination half-life of 6 hours. Blood samples were collected predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16 and 24 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

There was one drop-out (did not show up for period II). One adverse event (raised total and indirect bilirubin) was reported, which was not related to the study drug. Pharmacokinetic parameters were evaluated of the first 24 subjects completing the study in a cross-over design which is in accordance with the protocol.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, SD)) of metformine under fed conditions.

Treatment N=24	AUC _{0-t} µg.h/ml	AUC _{0-∞} µg.h/ml	C _{max} µg/ml	t _{max} h	t _{1/2} h
Test	11.2 ± 2.7	12.1 ± 2.7	1.27 ± 0.36	5 (2 - 8)	4.1 ± 0.7
Reference	10.9 ± 2.8	11.7 ± 2.8	1.22 ± 0.28	4.75 (1 - 8)	4.1 ± 0.6
*Ratio (90% CI)	1.03 (0.98 – 1.08)	1.03 (0.99 – 1.08)	1.04 (0.98 – 1.09)	---	---
CV (%)	10	9	11	---	---
AUC_{0-∞} 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					

**In-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 Aurobindo 850 mg film-coated tablets and the Glucophage 850 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 3 – 1000 mg

An open label, randomised, two-treatment, two sequence, two period, cross-over, single dose, comparative bioequivalence study was carried out under fed conditions in 26 healthy male volunteers, aged 18-45 years. After overnight fasting the subjects received an oral dose of 850 mg metformin (1 tablet) of either test or reference formulation with 240 ml of 20% glucose solution in water 30 minutes after taking a standardised high-fat, high caloric meal (approx 985 Kcal (60% fat, 25 % carbohydrate and 15% proteins) and was composed of 85 g fried eggs (282 Kcal), 26 g mutton curry (187 Kcal), 54 g bread slices with butter (205 Kcal), 45 g fried potatoes (169 Kcal), 240 mL milk (142 Kcal)). Subjects were given 60 ml of 20% glucose solution in water every 15 min for 4 hours after dosing. There were two dosing periods, separated by a washout period of at 13 days, which is sufficient for a compound with an estimated plasma elimination half-life of 6 hours. Blood samples were collected predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16 and 24 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

Four subjects were withdrawn due to adverse events (vomiting) during period I. One subject dropped-out of the study as he didn't show at the start of the second period. Eight adverse events occurred. A total of 5 adverse events (3 subjects after treatment with test and 2 with reference preparation) occurred during the study (vomiting 4 times; loose motion, 1 time) and led in 4 cases to withdrawal of the subject (all vomiting). All these adverse effects were considered (possibly) study related. The other 3 adverse events were post study laboratory test abnormalities, two of them were possible study drug related. All the adverse events were considered mild and resolved. A total of 21 subjects finished the study and pharmacokinetic parameters were evaluated of these 21 subjects.

Pharmacokinetic parameters were evaluated of the first 24 subjects completing the study in a cross-over design which is in accordance with the protocol.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{max} (median, SD)) of metformine under fed conditions.

Treatment N=21	AUC_{0-t} ng.h/ml	AUC_{0-∞} ng.h/ml	C_{max} ng/ml	t_{max} h	t_{1/2} h
Test	12771 (3813)	13189 (3876)	1464 (381.9)	4.5 (1.4)	---
Reference	131881 (3469)	13514 (3534)	1522 (447.3)	4.5 (1.4)	---
*Ratio (90% CI)	0.96 (0.90 – 1.04)	0.97 (0.91 – 1.04)	0.97 (0.87 – 1.09)	---	---
CV (%)	13.7	13.3	21.3	---	---

AUC_{0-∞}	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

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} 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 Aurobindo 1000 mg film-coated tablets 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.

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

Metformin was first approved in 1959, 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

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. A first test was performed with 10 participants. Due to the fact that most questions were answered correctly and the information could be found in most cases the leaflet was not rewritten or adjusted. A second run of 10 volunteers was performed with the same questions. The acceptance criteria of 16 or more volunteers answering each question correctly had been achieved, indicating that the information provided in the leaflet is acceptable.

The readability test itself and the evaluation report are of an acceptable quality. The conclusions are clear, concise and clearly presented. Furthermore, the following areas have been sufficiently covered: findability, understandability and applicability. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Metformine HCl Aurobindo 500 mg, 850 mg, and 1000 mg film-coated tablets a proven chemical-pharmaceutical quality and are a generic form of Glucophage 500 mg, 850 mg, and 1000 mg 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 pharmacovigilance system of the MAH was found to be insufficient. However, the MAH has committed not to place Metformine HCl Aurobindo film-coated tablets on the market in any of the Member states until the commitments regarding the pharmacovigilance system are fulfilled. Please see bottom of this page for these commitments.

The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. Metformine HCl Aurobindo 500 mg, 850 mg, and 1000 mg film-coated tablets were authorised in the Netherlands on 27 April 2006.

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 Aurobindo with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 5 December 2008.

A European harmonised birth date has been allocated (19 March 1959) and subsequently the first data lock point for metformin is April 2012, after which the PSUR submission cycle will be 3 years.

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

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

Quality - medicinal product

- The MAH has committed to carry out process validation for the manufacturing process of Metformin HCl tablets, when the first commercial scale batches of the drug product using Metformin HCl drug substance of one specific manufacturer are manufactured. The MAH also commits to carry out appropriate stability studies on these batches. The results of the above studies shall be held available at the manufacturing location for the inspectorate.
- The MAH has committed to provide the certificate of analysis for the first three batches of Metformin HCl tablets (manufactured using Metformin HCl from one specific site) to BfARM (Bundesinstitut für Arzneimittel und Medizinprodukte), prior to marketing those batches in Germany. The results shall be made available when these batches are manufactured based on commercial/demand requirements.
- The MAH has committed to provide the certificate of analysis for first three batches of Metformin Hydrochloride Tablets (manufactured using Metformin HCl from one specific site) to IMB (Irish Medicines Board), prior to marketing those batches in Ireland. The results shall be made available when these batches are manufactured based on commercial/demand requirements.

Pharmacovigilance

- The MAH has committed that prior to marketing, documented procedures will be in place and functioning for electronic reporting, responses to requests for information from regulatory authorities & meeting commitments to competent authorities in relation to marketing authorizations.
- The MAH has committed that prior to marketing, evidence of Eudravigilance registration will be submitted to all member states.
- The MAH has committed not to market the product until the MHRA finds the PV system complete, appropriate and functioning as per EU requirements.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BfARM	Bundesinstitut für Arzneimittel und Medizinprodukte
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
IMB	Irish Medicines Board
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 _{1/2}	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
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Secondary packaging site for all types of pharmaceutical forms.	NL/H/1459/001-003/IA/001	IA	3-4-2009	17-4-2009	Approval	N
Change in the name of the medicinal product in Italy,	NL/H/1459/001-003/IB/002	IB	3-4-2009	3-5-2009	Approval	N
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/1459/001-003/IA/003	IA	28-4-2009	12-5-2009	Approval	N
Change in the name of the medicinal product in France.	NL/H/1459/001-003/IB/004	IB	6-5-2009	5-6-2009	Approval	N
Deletion of any manufacturing site (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place).	NL/H/1459/001-003/IA/005	IA	20-5-2009	3-6-2009	Approval	N
Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release, not including batch control/testing.	NL/H/1459/001-003/IA/006	IA	28-5-2009	11-6-2009	Approval	N
Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release, not including batch control/testing.	NL/H/1459/001-003/IA/007	IA	28-5-2009	11-6-2009	Approval	N
Change in the name of the medicinal product in Finland and Sweden.	NL/H/1459/001-003/IB/008	IB	12-8-2009	10-9-2009	Approval	N
Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release, including batch control/testing.	NL/H/1459/001-003/IA/009	IA	14-8-2009	28-8-2009	Approval	N