CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Fertin 1 mg, 2 mg, 3 mg and 4 mg, tablets
Medochemie Limited, Cyprus

glimepiride

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/1229/001-004/DC
Registration number in the Netherlands: RVG 101205-101208

19 April 2010

Pharmacotherapeutic group:	sulfonamides, urea derivatives
ATC code:	A10BB12
Route of administration:	oral
Therapeutic indication:	type 2 diabetes mellitus, when diet, physical exercise and weight reduction alone are not adequate
Prescription status:	prescription only
Date of authorisation in NL:	10 December 2009
Concerned Member States:	Decentralised procedure with BG (1, 2 and 3 mg only) and CY, CZ, LV (all strengths)
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 Fertin 1 mg, 2 mg, 3 mg and 4 mg, tablets, from Medochemie Limited. The date of authorisation was on 10 December 2009 in the Netherlands. The product is indicated for type 2 diabetes mellitus, when diet, physical exercise and weight reduction alone are not adequate.

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

Glimepiride is an orally active hypoglycaemic substance belonging to the sulphonylurea group. It may be used in non-insulin dependent diabetes mellitus.
Glimepiride acts mainly by stimulating insulin release from pancreatic beta cells. As with other sulphonylureas this effect is based on an increase of responsiveness of the pancreatic beta cells to the physiological glucose stimulus. In addition, glimepiride seems to have extrapancreatic effects also postulated for other sulphonylureas.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Amaryl 1, 2, 3 and 4 mg (NL RVG 17843-17846) which have been registered in the Netherlands by Sanofi-Aventis Netherlands B.V. since 20 June 1995. In addition, reference is made to Amaryl authorisations in the individual member states (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 a bioequivalence study in which the pharmacokinetic profile of the 4 mg product is compared with the pharmacokinetic profile of the reference product Amaryl 4 mg tablets, registered in the UK. 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 products.

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 a generic application.

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 these product types 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 glimepiride, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is practically insoluble in water, soluble in dimethyl

formamide, slightly soluble in methylene chloride and very slightly soluble in methanol. Glimepiride exhibits polymorphism; form 1 is manufactured. Glimepiride has a chemical structure that two trans enantiomers and two cis enantiomers are possible.

The Active Substance Master File (ASMF) procedure is used for both suppliers of 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
Description of manufacturing process and process control is included in the DMF. Criteria for acceptance are given in the Restricted Part.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur., with the exception of loss on drying. A cross validation of loss on drying and water content has been provided, demonstrating that the inclusion of loss on drying in the specification is acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for four full-scale batches. The polymorphic form of glimepiride is confirmed by XRD, FTIR and DSC analysis.

Stability of drug substance
For one supplier, stability data on the active substance have been provided for three full-scale batches stored at 25°C/60% RH (48 months) and 40°C/75% RH (6 months). The batches were adequately stored. No specific up or downward trend was observed in any of the parameters tested.
For the other active substance supplier, stability data have been provided for seven full-scale batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months). No changes were observed.
Based on the results provided, a retest period of 24 months could be granted with no special storage conditions.

** 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
Fertin 1, 2, 3 and 4 mg, tablets contain as active substance 1 mg, 2 mg, 3 mg or 4 mg glimepiride, respectively.

Fertin 1 mg is pink, round, flat, scored on one side tablet with diameter 6mm.
Fertin 2 mg is green, oval, flat, scored on one side, embossed "MC" on the other side tablet with dimensions 5x10mm.
Fertin 3 mg is pale yellow, oval, flat, scored on one side, embossed "MC" on the other side tablet with dimensions 5x10mm.
Fertin 4 mg is blue, oval, flat, scored on one side, embossed "MC" on the other side tablet with dimensions 5x10mm.

The tablets are packed in PVC/PVDC/Aluminium blister packs.

The excipients are: lactose monohydrate, sodium starch glycolate (type A), povidone (K30), magnesium stearate. Coloring agents: 1 mg - red iron oxide (E172), 2 mg - yellow iron oxide (E172), indigo carmine (E132), 3 mg - yellow iron oxide (E172), 4 mg - indigo carmine (E132).

The 1 mg and 2 mg strength tablets are dose proportional with exception of the colorants. The 2, 3 and 4 mg strengths are practically the same with the exception of the used active substance. The difference in amount of active substance is compensated by lactose monohydrate.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The excipients and packaging are usual for this type of dosage form.
The product development was based on the composition of the 1 mg strength and a dose proportional approach was adopted for 2, 3 and 4 mg strengths. The dissolution profiles of the bio-batch and Amaryl tablets are considered to be comparative.
A comparative dissolution profile of the Dutch reference product has been presented, demonstrating that the UK reference product is also representative for the reference products on the Dutch market.
Comparative dissolution profiles of the Dutch reference product and the products registered in the CMSs were also presented.
The pharmaceutical development has been described in sufficient detail.

Manufacturing process
The tablets are produced using a well-established manufacturing process: wet granulation and subsequent compression. Acceptable process validation protocols were presented for all strengths and batch sizes. The product is manufactured using conventional manufacturing techniques, but the drug substance content is below 2%, making it a non-standard process. Process validation data on the product have been presented on eight full-scale batches based on a bracketing approach. A commitment was made to include an additional batch in order to complete process validation.

Control of excipients
The excipients comply with Ph.Eur., except for the used colorants which comply with in-house specifications. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, average weight, disintegration, hardness, friability, identification by HPLC and UV, loss on drying, dissolution, related substances, content uniformity, assay and microbial control. Release and shelf-life limits are identical. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on six batches, demonstrating compliance with the release specification. The data of at least three full-scale batches of each strength have been presented.

Stability of drug product
Given the dose proportionality of the 1 mg and 2 mg tablet strength and the fact that the 2 mg, 3 mg and 4 mg strengths are practically the same with regard to the formulation and composition, a bracketing approach was used for the stability study. Two batches of the 1 mg and 4 mg and one batch of the 2 mg and 3 mg tablets were included in the stability studies. Stability data on the product has been provided for six full-scale batches stored at 25°C/60% RH (18 months) and at 40°C/75% RH (6 months). Five batches were also stored at 30°C/ 65% RH (18 months). The conditions used in the stability studies are according to the ICH stability guideline. The tablets were stored in PVC/PVDC-Al blisters. Furthermore a photostability test was performed, demonstrating that the product is photostable. Based on the results, a shelf-life of 24 months with no special storage conditions could be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Magnesium stearate is derived from a vegetable source. Lactose monohydrate is produced from milk sourced from healthy animals. Assurances and certification in this respect have been presented.

II.2 Non clinical aspects

These products are generic formulations of Amaryl, 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 glimepiride 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

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

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Fertin 4 mg (Medochemie Limited, Cyprus) is compared with the pharmacokinetic profile of the reference product Amaryl 4 mg tablets (Hoechst Marion Roussel, UK).

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 manufacturer of the finished product used in the bio-equivalence study is not the same as the manufacturer of the finished product responsible for the product to be marketed. Changes with regard to the finished product manufacturer might result in possible differences in bioavailability, which subsequently may result in therapeutic inequivalence. Therefore bridging to the to-be marketed medicinal product is considered required. In accordance with the Q&A by the QWP, published in July 2008 (http://www.emea.europa.eu/Inspections/qwp/q24.htm), it has sufficiently been be demonstrated by the MAH that the bioequivalence batch is representative of the industrial scale product to be marketed, as the difference between the two tablets manufactured at the different sites is negligible.

Design
An open-label, single blind, balanced, randomised, two treatment, two period, two sequence, single dose, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 18-40 years. Each subject received a single dose (4 mg) of one of the 2 glimepiride formulations. The tablet was orally administered with 240 ml water after a supervised overnight fast of at least 10 hours.
Except for water given with the study medication, no fluids were allowed from 1 hour before dosing until 2 hour post dose. Meal plans were identical for both periods. There were 2 dosing periods, separated by a washout period of 10 days.

Blood samples were collected in heparin blood tubes pre-dose and at 0.25, 0.5, 1.0, 1.5, 2.0, 2.25, 2.5, 2.75, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 18.0, 24.0, 30.0 and 36.0 hours after administration of the products. Subjects were monitored for their blood glucose levels pre-dose and at regular intervals up to 4 hours post-dose.

Analytical/statistical methods
The analytical method has been adequately validated and is 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 36 volunteers completed the two study periods and were used for statistical analyses as per protocol.

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

Treatment N=36	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	2255 ± 1535	2485 ± 2606	330 ± 96	3.0 (1.0 – 5.0)	6.4 ± 3.7
Reference	2257 ± 1720	2473 ± 2708	346 ± 105	3.0 (1.5 - 5.0)	6.7 ± 3.7
***Ratio (90% CI)**	101.2 (97.2 – 105.2)	101.1 (97.2 – 105.2)	95.7 (89.5 – 102.2)	-	-
CV (%)	10.0	10.0	16.9	-	-

$AUC_{0-\infty}$ 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 glimepiride under fasted conditions, it can be concluded that Fertin 4 mg and Amaryl 4 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.

Glimepiride may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of glimepiride. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Extrapolation to other strengths
Bioequivalence can be extrapolated to other tablet strengths (e.g. 1 mg, 2 mg and 3 mg) since:
- The different strengths are manufactured by the same manufacturer and manufacturing process
- Drug input is linear over the therapeutic dose range.
- Qualitative compositions of the different strengths are the same with the exception of the colourants.
- The concentration of the active substance is below 5% and the ratio between the amounts of excipients is practically similar. The 1 mg and 2 mg tablets are dose proportional.
- The dissolution profiles are similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalene study. The dissolution profiles demonstrate that the drug product dissolved for more than 85% within 10 minutes.

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
Glimepiride was first approved in 1995, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of glimepiride 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. The test consisted of a pilot test with 2 participants, followed by three rounds with 10 participants each. The composition of the subject population was acceptable for age, gender and education. The developed questionnaire contained 19 questions specific to the products and to the format of the package leaflet. The questions all addressed the key safety issues and concerns of Fertin tablets. The technical readability, comprehensibility of the text, traceability of information and the applicability were investigated during the test. Safety issues specific to this kind of tablets were addressed using questions that used imaginary situations to verify that the participants understood and were able to apply the information to make the correct decision.

During the first round, positive and negative feedback was received from each of the 10 participants. Problem areas of the PIL were identified, after which the PIL was adapted. The changes made as a result of the first testing round are clearly indicated in the user test report. The amended PIL was used in the second round of testing.

The second test round led to further comments and suggestions for adaption of the PIL. The quantitative and qualitative results were processed and analysed. This did not result in further revisions.

Finally, the third test round was performed, which also did not lead to revisions of the PIL.

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. Furthermore, 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

Fertin 1 mg, 2 mg, 3 mg and 4 mg, tablets have a proven chemical-pharmaceutical quality and are generic forms of Amaryl tablets. Amaryl 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, package leaflet and labelling are in the agreed templates and are in agreement with other glimepiride 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 Fertin 1 mg, 2 mg, 3 mg and 4 mg, tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 4 February 2009. Fertin 1 mg, 2 mg, 3 mg and 4 mg, tablets were authorised in the Netherlands on 10 December 2009.

A European harmonised birth date has been allocated (20 June 1995) and subsequently the first data lock point for glimepiride is June 2009. The first PSUR for Fertin will be submitted with a data lock point of June 2012, accompanied by an addendum report covering the period between day 210 of this DCP, namely 4 February 2009, and the DLP of June 2009.

The date for the first renewal will be: 28 February 2013.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The applicant committed to complete the process validation of all three validation batches for each strength within the first year after marketing authorisations are granted.

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