CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Telmisartan-1A Pharma 20 mg, 40 mg, and 80 mg tablets
1A Pharma GmbH, Germany

telmisartan

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/1803/001- 003/DC
Registration number in the Netherlands: RVG 105920,105923-4

7 April 2011

Pharmacotherapeutic group:	angiotensin II antagonists, plain
ATC code:	C09CA07
Route of administration:	oral
Therapeutic indication:	treatment of essential hypertension in adults; Reduction of cardiovascular morbidity in patients with: i) manifest atherothrombotic cardiovascular disease or ii) type 2 diabetes mellitus with documented target organ damage
Prescription status:	prescription only
Date of authorisation in NL:	22 February 2011
Concerned Member States:	Decentralised procedure with DE
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

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

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Telmisartan-1A Pharma 20 mg, 40 mg, and 80 mg tablets, from 1A Pharma GmbH. The date of authorisation was on 22 February 2011 in the Netherlands. The product is indicated for:

Hypertension:
Treatment of essential hypertension in adults.

Cardiovascular prevention:
Reduction of cardiovascular morbidity in patients with:
i) manifest atherothrombotic cardiovascular disease (history of coronary heart disease, stroke, or peripheral arterial disease) or,
ii) type 2 diabetes mellitus with documented target organ damage.

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

Telmisartan is an orally active and specific angiotensin II receptor (type AT_1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptor. Telmisartan selectively binds the AT_1 receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT_2 and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore it is not expected to potentiate bradykinin-mediated adverse effects.

This decentralised procedure concerns a generic application claiming essential similarity with Micardis 20 mg, 40 mg, and 80 mg (EU License EU/1/98/090) which have been registered through a centralised procedure by Boehringer International GmbH Germany since 1998).

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 one bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Micardis 80 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 telmisartan, an active substance described in the European Pharmacopoeia (Ph. Eur.*). The active substance is practically insoluble in water, slightly soluble in methanol, sparingly soluble in methylene chloride and it dissolves in 1M sodium hydroxide. Telmisartan shows polymorphism and polymorphic form A is used in this dossier.

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

Manufacture
For both manufacturers the manufacturing process has been sufficiently described.

Quality control of drug substance
The MAH included one drug substance specification in line with the Ph.Eur. with additional tests and limits per drug substance manufacturer. The drug substance specification consists of: description, identification, colour of solution, loss on drying, sulphated ash, related substances and assay. The additional tests concerned residual solvents. Since different impurities were included in the specification of one of the manufacturers, an additional test was included to limit those impurities.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for two full scaled batches from one manufacturer, and for one full scaled batch from the other manufacturer.

Stability of drug substance
First manufacturer - Stability data on the active substance have been provided for 3 full scaled and 3 pilot scaled batches stored at 25°C/60% RH (max. 36 months) and 40°C/75% RH (6 months). The batches were adequately stored. No changes were observed. The proposed retest period of 36 months without special storage conditions packaged in the double polyethylene bags placed in a HDPE drum can be granted.

Second manufacturer - Stability data on the active substance of have been provided for 3 full scaled batches stored at 25°C/60% RH (max. 24 months) and 40°C/75% RH (6 months). The batches were adequately stored. No changes were observed. The proposed retest period of 36 months without special storage conditions packaged in the double polyethylene bags placed in a HDPE drum can be granted.

** 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
Telmisartan-1A Pharma 20 mg are white, round, plain tablets, debossed with '*20'* on one side.
Telmisartan-1A Pharma 40 mg are white, oblong, plain tablet, scored on one side and debossed with '*40'* on the other side.
Telmisartan-1A Pharma 80 mg are white, oblong, plain tablet, scored on one side and debossed with '80' on the other side.

The excipients are - sodium hydroxide, meglumine, povidone K25, lactose monohydrate, povidone, crospovidone, lactose anhydrous and magnesium stearate.

The excipients and packaging are usual for this type of dosage form.
The tablets are packed in Al/Al blisters. Telmisartan tablets 20 mg, 40 mg and 80 mg are dose-weight proportional in terms of all excipients.

Container closure system
Telmisartan-1A Pharma tablets, 20 mg, 40 mg and 80 mg are packed into polyamide-Al-PVC / acrylate-Al-PVC blister packaging. Specifications, control procedures, certificates of analysis and IR-spectra of the Al-foils are included in the dossier and are considered to be acceptable. The packaging material is in line with the Directive 72/2002/EC and Ph.Eur. 3.1.11 *Materials based on non-plasticised poly(vinyl chloride) for containers for dry dosage forms for oral administration.* The packaging material is well described and acceptable for the packaging of the drug product.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Final formulation and the process were optimized on laboratory scale batches and further on a small production scale.

In-vitro studies have been performed in order to develop the dissolution method as included in the specification. A biobatch was produced. The applicant adequately demonstrated that the reference and test product are pharmaceutically equivalent to each other.

Manufacturing process
The manufacturing process consist of the following steps: Granulation, blending and compression.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 10 full scaled batches (at least 3 per strength). The product is manufactured using conventional manufacturing techniques.

Quality control of drug product
The product specification includes tests for appearance, water content, identification, assay, uniformity of dosage units, dissolution, related substances, residual solvents and microbial quality.
The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on the same 10 full scaled batches as the batches used for the validation of the manufacturing process. Compliance with the release specification has been demonstrated.
The MAH has committed to demonstrate compliance with the specification by producing a batch of Telmisartan-1A Pharma tablets applying the maximum holding times for the final blend and the tablets in bulk.

Stability of drug product
Stability data on the product has been provided three full scaled batches per strength batches stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in an Al/Al blister. A decrease in assay was observed and no increase in impurities at both long term and accelerated conditions. This was due to the variability in the potentiometric assay method

The proposed shelf-life of 2 years when stored in the original packaging in order to protect from moisture can be granted.
The MAH has committed to continue the stability study at least until the end of the applied shelf-life on the production batches already included in the study.

Holding time
The proposed holding time for the bulk tablets was 12 months when stored in Al bag. Up to 12 months of stability data were available. No trends or out of specification results were observed. Therefore the bulk shelf-life of 12 months stored in an Al-bag below 25°C was granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose is of animal origin. The suppliers confirm that the milk used for the production of lactose is derived from healthy animals and is collected under the same conditions as milk for human consumption. Magnesium stearate is from vegetable origin.

II.2 Non clinical aspects

This product is a generic formulation of Micardis 20 mg, 40 mg, and 80 mg tablets, which are 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 telmisartan 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

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

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Telmisartan-1A Pharma 80 mg tablets (1A Pharma GmbH, Germany) compared with the pharmacokinetic profile of the reference product Micardis 80 mg tablets (Boehringer Ingelheim International GmbH, Germany).

Micardis tablets are registered via the centralised procedure and hence are presumed to be identical in all member states of the EEA.

The study was conducted in accordance with GLP. No major deviations from the protocol were observed. On Day 145, one of the Member States questioned the GCP status of the CRO, based on an inspection of this CRO by the MHRA in April 2010. However, it is agreed by all Member States that the outstanding issues concerning the CRO as a result of this inspection are considered not directly related to the reliability of the results of the submitted bioequivalence study.

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

Bioequivalence study
A open label, randomised, two-treatment, two-sequence, four period, crossover, single-dose, replicate, comparative oral bioequivalence was carried out under fasted conditions in 36 healthy male and female subjects, aged 22-49 years. A randomisation scheme was included in the report. Subjects were randomized equally into two sequence groups: ABAB or BABA. Each subject was scheduled to receive a total of two treatments (each treatment twice) by the end of the study. The tablet was orally administered

with 240 ml water after a 10 hour fasting period. For each subject the dosing periods were separated by a washout period of 14 days.

Blood samples were collected predose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 8, 12, 24, 36, 48, 72 and 96 hours after administration of the products.
During the procedure there was some discussion on the the analytical methods used. It was concluded that the analytical method was 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.

Rationale for a four-period BE study
The aim of performing a bioequivalence study with a four period study design was to define the within-subject variability for C_{max} of the reference product as accurate as possible. In study with this design each subject receives the test and reference product twice, which provided enough reliable data to calculate the accurate value of coefficient of variability. Results from this study confirmed data from literature that telmisartan is a highly variable drug with CV 36.2%.

Telmisartan may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of telmisartan. 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.

Results
Seven subjects dropped out the study; three subjects voluntarily withdrew (2 for emergencies and 1 did not show for check in) four were dismissed from the study (2 for positive drugs of abuse test, 1 due to low haemoglobin and 1 for a very late check in and as result of this no safety sample could be obtained). The seven subjects were not replaced. The data of 36 volunteers were used for safety analysis. The samples of the 29 volunteers who completed the study were analyzed statistically.

Adeverse events
A total of 16 mild AEs were experienced by the subjects after taking the test product; of these events 9 were suspected drug reactions, the other events were assessed as non related. A total of 6 mild AEs were experienced by the subjects after taking the reference product of these events 2 were suspected drug reactions. No serious adverse events were reported during the conduct of this study. Both the test product and reference product were well tolerated by all subjects.

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

Treatment **N = 29**	**AUC_{0-t}** ng*.h/ml	**$AUC_{0-\infty}$** ng*.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1958 ± 1458	2147 ± 1551	354 ± 314	0.92 (0.33-5)	21 ± 8
Reference	2057 ± 1519	2199 ± 1773	376 ± 268	1.00 (0.5-2.5)	22 ± 11
*Ratio (90% CI)	0.96 (0.90-1.03)	0.96 (91-1.03)	0.91 (0.80-1.04)	---	---
CV (%) Global (test) Global (ref)	 23 20	 22 17	 53 36	---	---

$AUC_{0-\infty}$ 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 telmisartan under fasted conditions, it can be concluded that Telmisartan-1A Pharma 80 mg tablets and Micardis 80 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation of results
The following conditions for a biowaiver were met:
The pharmaceutical products are manufactured by the same manufacturer and process.

- The composition of the different strengths was dose proportional
- The ratio between amounts of the active substance and excipients is the same, or, in the case of preparations containing a low concentration of the active substance (less than 5%), the ratio between the amount of excipients is similar
- The dissolution profiles are similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study.

Therefore, the results of the bioequivalence study performed with the 80 mg tablets also apply to the other 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
Telmisartan was first approved in 1998, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of telmisartan 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 final SPC is in line with the leaflet of the Centralised approved innovator product Micardis EU/1/98/090.

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 evaluation report of the test is of an acceptable quality. The conclusions are clear, concise and clearly presented.

The test consisted of two rounds with 10 participants each. Inclusion and exclusion criteria of the test persons were specified in the protocol. The test was performed in English. Educational levels correspond with the inclusion criteria set in the protocol.
The test was performed by face-to-face interviews. Questions were designed to determine whether users can identify key information that is necessary for appropriate use.
There were sufficient questions about the critical sections and the areas traceability, comprehensibility and applicability were sufficiently covered. The test included 16 questions related to the content of the PL. Three questions were related to the structure/appearance of the PL.
Participants were interviewed individually by one experienced and trained interviewer. A second interviewer also observed the behaviour of the participant. The responses were digitally recorded and

written down by hand. A satisfactory outcome was achieved when 90% of the participants were able to find information and answer each question correctly.
In round 1, at least 90% of the time the correct section was located to answer the question. Each question was correctly answered 100% of the time. No adjustments to the package leaflet were made between the first and the second round. In the second round 90% of the participants were able to locate the section and 100% were able to answer the questions. Therefore no further changes were considered to be required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Telmisartan-1A Pharma 20 mg, 40 mg, and 80 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Micardis 20 mg, 40 mg, and 80 mg. Micardis is a well-known medicinal product with an established favourable efficacy and safety profile.

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

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

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

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Telmisartan-1A Pharma 20 mg, 40 mg, and 80 mg tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 12 October 2010. Telmisartan-1A Pharma 20 mg, 40 mg, and 80 mg tablets are authorised in the Netherlands on 22 February 2011.

The first PSUR for these products, covering the period of a year, namely 12 October 2010 until 12 October 2011, will be submitted not later than 60 days from data lock point 12 October 2011.
The common renewal date is five years after D210 of the DCPs, namely 12 October 2015.

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

Quality - active substance

- The MAH has committed to continue the stability study at least until the end of the applied shelf-life on the production batches already included in the study.
- The MAH has committed to demonstrate compliance with the specification by producing a batch of Telmisartan-1A Pharma tablets applying the maximum holding times for the final blend and the tablets in bulk.

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