CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Telmisartan/Hydrochloorthiazide Sandoz 40/12.5 mg, 80/12.5 mg and 80/25 mg, coated tablets Sandoz B.V., the Netherlands

telmisartan/hydrochlorothiazide

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/2604/001-003/DC
Registration number in the Netherlands: RVG 111922-111924

20 November 2013

Pharmacotherapeutic group:	angiotensin II antagonists and diuretics
ATC code:	C09DA07
Route of administration:	oral
Therapeutic indication:	essential hypertension
Prescription status:	prescription only
Date of authorisation in NL:	5 November 2013
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/Hydrochloorthiazide Sandoz 40/12.5 mg, 80/12.5 mg and 80/25 mg, coated tablets from Sandoz B.V. The date of authorisation was on 5 November 2013 in the Netherlands.

The product is indicated for treatment of essential hypertension.
The fixed dose combinations of 40 mg telmisartan/12.5 mg hydrochlorothiazide and 80 mg telmisartan/12.5 mg hydrochlorothiazide are indicated in adults whose blood pressure is not adequately controlled on telmisartan alone.
The fixed dose combination of 80 mg telmisartan/25 mg hydrochlorothiazide is indicated in adults whose blood pressure is not adequately controlled on 80 mg/12.5 mg or adults who have been previously stabilised on telmisartan and hydrochlorothiazide given separately.

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

Telmisartan is an orally active angiotensin II receptor antagonist. Angiotensin II has an important role in the renin-angiotensin system by stimulation of the sympathetic activity, arteriolar vasoconstriction and water and salt retention. These effects result in an increase in blood pressure. Treatment with an angiotensin type 2 antagonist blocks this action and is therefore indicated for essential hypertension and renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive medical product regimen.
Hydrochlorothiazide is a thiazide diuretic. It affects electrolyte reabsorption mechanisms in the kidney, by inhibition of the Na^+Cl^- symporter. The increased sodium and chloride excretion will result in a decreased plasma volume. The resulting plasma renin activity, aldosterone secretion and urinary potassium excretion is partially mediated by angiotensin II.
The combination of telmisartan and hydrochlorothiazide has an additive effect, reducing the blood pressure more than either medicine alone. By lowering the blood pressure, the risks associated with high blood pressure, such as having a stroke, are reduced.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Micardis Plus 40 mg/12.5 mg, 80 mg/12.5 mg and 80 mg/25 mg tablets, registered since 19 April 2002 by Boehringer Ingelheim through a centralized procedure (MA numbers EU/1/02/213/001-023).

The marketing authorisation is granted based on article 10(1) 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 product is compared with the pharmacokinetic profile of the reference product Micardis Plus 80 mg/25 mg tablets, registered in the EEA. 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 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 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 substances
The active substances are telmisartan and hydrochlorothiazide, established active substances described in the European Pharmacopoeia (Ph.Eur.*). Telmisartan is a white or slightly yellowish crystalline powder, which is practically insoluble in water. The polymorphic form of telmisartan is Form A. Hydrochlorothiazide is a white to almost white crystalline powder and is very slightly soluble in water. The polymorphic form of hydrochlorothiazide is Form I.

The CEP procedure is used for the two active substances. 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 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.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

** 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.*

Telmisartan
Quality control of drug substance
The drug substance specification is in line with the CEPs, with additional requirements for residual solvents. The specification is acceptable for both sources in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for two full-scale batches of each supplier.

Stability of drug substance
The active substance is stable for 4 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Hydrochlorothiazide
Quality control of drug substance
The drug substance specification is in line with the CEPs, with additional requirements for particle size. The specification is acceptable for both sources in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for two full-scale batches of each supplier.

Stability of drug substance
The active substance is stable for 3 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Medicinal Product

Composition
Telmisartan/Hydrochloorthiazide Sandoz 40/12.5 mg is a red, oval, biconvex coated tablet debossed with 40 on one side and with 12.5 on the other side
Telmisartan/Hydrochloorthiazide Sandoz 80/12.5 mg is a white to off-white, oval, biconvex coated tablet debossed with 80 on one side and with 12.5 on the other side.
Telmisartan/Hydrochloorthiazide Sandoz 80/25 mg is a yellow, oval, biconvex coated tablet debossed with 80 on one side and with 25 on the other side.

The coated tablets are packed in Al/Al blisters.

The excipients are:
Tablet core - sodium hydroxide, meglumine, povidone K25 (E1201), lactose monohydrate, povidone K30 (E1201), crospovidone (type A) (E1202), lactose anhydrous, magnesium stearate (E572)
Coating - polivinyl alcohol units (E1203), polyethylene glycol (E1521), anhydrous colloidal silica (E551), citric acid monohydrate (E330), iron oxide yellow (E172) (40/12.5 mg + 80/25 mg); iron oxide red (E172) (40/12.5 mg).

The 40 mg/12.5 mg and the 80 mg/25 mg strength are dose proportional. The sub-coated tablets of all strengths are fully dose proportional. The 80 mg/12.5 mg strength differs with respect to the coating containing hydrochlorothiazide.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The drug product consists of a core tablet that contains telmisartan, a sub-coating and a coating which contains hydrochlorothiazide. The main development studies were formulation trials and manufacturing scale-up and optimisation trials. Formulation trials were performed to investigate the effect of the excipient amounts. Manufacturing scale-up and optimisation trials were performed to determine the optimal process parameters and the amount of overage of coating solution needed. Content uniformity and assay of hydrochlorothiazide were concluded to be critical quality attributes.
The batch used in the bioequivalence study has the same composition and is manufactured in the same way as the future commercial batches. The bioequivalence batch is of sufficient size in relation to the intended commercial batch size. The bioequivalence study was performed against the German reference product. This is acceptable, as the originator product has been registered through a centralised procedure. The MAH demonstrated comparable dissolution profiles for telmisartan hydrochlorothiazide tablets 80 mg/25 mg compared to 80 mg/12.5 mg and 40 mg/12.5 mg. The pharmaceutical development of the product has not been adequately performed.

Manufacturing process
The manufacturing process is divided into wet granulation, blending, lubrication, compression, sub-coating, coating and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full batches of each strength manufactured at both manufacturing sites.

Control of excipients
The excipients comply with relevant Ph.Eur. monographs, except for iron oxide which complies with the USP/NF monograph. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification of both drug substances and colorants, water content, assay of both drug substances, content uniformity of both drug substances, dissolution of both substances, related substances, ethanol content and microbial quality. The release and shelf-life limits are identical except for assay and related substances. The drug product specification is acceptable.

The analytical methods have been adequately described and validated. Batch analytical data from both production sites have been provided on three full-scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided three full-scale batches of each strength stored at 25°C/60% RH (24-36 months) and at 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 Al/Al blisters.
At accelerated conditions increases in related substances were observed in all tablet strengths, however the increases were more pronounced in the 80 mg/12.5 mg tablet. At long term conditions the results of related substances were variable, but a slight upward trend could be observed. All results remained within the specification limits. Three months stability data of batches manufactured at the second production site show a similar stability profile.
Photostability studies have been performed on one batch of 80 mg/12.5 mg tablets in accordance with 'Note for Guidance on the Photostability Testing of New active substances and Medicinal Products'. The tablets were directly exposed. No changes were observed in description and related substances.
Based on the provided stability data the proposed shelf life of 24 months can be granted, with the applicable storage condition 'Store in original blister, in order to protect from moisture. This medicinal product does not require any special temperature storage conditions'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The only excipients of animal origin are except for lactose anhydrous and lactose monohydrate. Declarations have been provided stating that these excipients have been prepared in accordance with the current version of the Note for Guidance EMEA/410/01. Magnesium stearate is of vegetable origin.

II.2 Non-clinical aspects

This product is a generic formulation of Micardis Plus, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

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 or hydrochlorothiazide 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 and hydrochlorothiazide are well-known active substances with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Telmisartan/Hydrochloorthiazide Sandoz 80/25 mg (Sandoz B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Micardis Plus 80/25 mg tablets (Boehringer Ingelheim International GmbH, Germany).

The choice of the reference product
The choice of the reference product in the bioequivalence study is justified, as it has been registered through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, randomised, two-treatment, partial replicate design bioequivalence study was carried out under fasted conditions in 42 healthy male and female subjects, aged 18-55 years. Subjects were randomly assigned to one of the 3 dosing sequences ABB, BAB or BBA (A = test, B = reference).
Single doses of 80/25 mg were administered. There were 3 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 14, 24, 36 and 48 hours after administration of the products.

The design of this study is acceptable. The partial replicate design was chosen to support the claim for high intra-subject variation and widened acceptance criteria. This is acceptable. The sampling scheme is adequate for both compounds.

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 reasons for drop-out were documented; prior to period 2 there were drop-outs due to adverse events (3) and due to suspicion of participation in multiple clinical trials (2). Prior to the third period there was 1 drop-out due to an adverse event. Thirty-six subjects completed the study. An additional subject finished 2 of the 3 study periods and therefore a total of 37 subjects were included in the pharmacokinetic and statistical analysis.

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

Treatment N=37	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1659 ± 1173	1838 ± 1273	362 ± 323	1.0 (0.5-3.0)	--
Reference	1603 ± 1091	1743 ± 1183	333 ± 329	0.83 (0.5-4.0)	--
***Ratio (90% CI)**	1.02 (0.98-1.07)	1.05 (1.00-1.10)	1.05 (0.93-1.18)	--	--

$AUC_{0-\infty}$ 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*

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

Treatment N=37	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1185 ± 456	1216 ± 466	180 ± 70	1.25 (1.0-3.0)	--
Reference	1155 ± 406	1187 ± 414	168 ± 62	1.5 (1.0-4.0)	--

***Ratio (90% CI)**	1.02 (1.00-1.05)	1.02 (1.00-1.05)	1.06 (1.01-1.12)	--	--

$AUC_{0-\infty}$ 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 and hydrochlorothiazide under fasted conditions, it can be concluded that Telmisartan/Hydrochloorthiazide Sandoz 80/25 mg and Micardis Plus 80/25 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.

For two subjects more than 20% extrapolated AUC values of telmisartan were observed, but this does not lead to suspect improper characterisation of the pharmacokinetic profile. Visual inspection of these profiles confirm an adequate time schedule to cover the AUC. Deviations of the $AUC_{0-\infty}$ are more likely to be a result of improper characterisation of the elimination phase.
A pre-dose level was detected for one subject in the first period. However, as the observed value was very low, it is not expected to influence the pharmacokinetic characterisation of the administered formulation. Therefore it is not likely to influence the bioequivalence conclusion.

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

Biowaiver
The MAH proposed a biowaiver for the two other strengths: 40/12.5 mg and 80/12.5 mg. The highest strength tablet has been used for the bioequivalence study. Therefore non-linearity for telmisartan is not an issue for the acceptance of the biowaiver.
Furthermore, guideline compliance is agreed for the manufacturing process and the qualitative composition of the different strengths. The biowaiver for the 40/12.5 mg strength is agreed .This is not agreed for the quantitative proportionality of the 80 mg/12.5 mg and 80 mg/25 mg strengths. The 80/12.5 mg and the 80/ 25 mg strengths differ only in coating, as the tablet cores are identical. The argumentation of the MAH that immediate release formulations coating components are exempted from the guideline is not agreed, as the guideline is not intended for formulations in which the active component is integrated in to the tablet coating.
However, as rapid dissolution of hydrochlorothiazide has been demonstrated for these formulations and in view of the BCS classification of this substance, clinical implications of this guideline deviation are expected to be minimal or absent.
Additionally, comparable dissolution was demonstrated between the different strengths applied for. Therefore, the biowaiver for the 2 additional strengths is acceptable.

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
The combination of telmisartan and hydrochlorothiazide was first approved in 2002, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of telmisartan and hydrochlorothiazide can be considered to be well established and no product specific

pharmacovigilance issues were identified pre- or post authorisation 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 proposed SPC is considered acceptable. Besides the chemical-pharmaceutical information, the SPC is identical to that of the centrally approved innovator product Micardis Plus EU/1/02/213 (version February 2013).

Readability test
The package leaflet has not been evaluated via a user consultation study. In MAH's view, readability for the PL of this product is assured by:

- using the package leaflet, which derives from the EPAR – Product Information for Micardis Plus last updated in February 2012. As stated in the accompanying Scientific Discussion (WC500028552) the CHMP considered that the user testing provided for Micardis Plus was adherent to the EC Guideline and the results reported met the readability success criteria.
- applying Sandoz layout, for which user friendliness has been demonstrated in several previously performed user tests. Reference to specific tests has been submitted as well as mock-ups for current PL and the tested PL

It is agreed with the MAH that the content of the PL does not require separate user testing.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Telmisartan/Hydrochloorthiazide Sandoz 40/12.5 mg, 80/12.5 mg and 80/25 mg, coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Micardis Plus 40 mg/12.5 mg, 80 mg/12.5 mg and 80 mg/25 mg tablets. Micardis Plus 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 member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Telmisartan/Hydrochloorthiazide Sandoz 40/12.5 mg, 80/12.5 mg and 80/25 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 15 May 2013. Telmisartan/Hydrochloorthiazide Sandoz 40/12.5 mg, 80/12.5 mg and 80/25 mg, coated tablets were authorised in the Netherlands on 5 November 2013.

The date for the first renewal will be: 15 May 2018.

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

Quality - medicinal product

- The MAH committed to continue the on-going long-term stability studies as per provided study design (*i.e.* up to 36 months).

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