EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 February 2013
EMA/84367/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tolucombi

International non-proprietary name: telmisartan/hydrochlorothiazide

Procedure No. EMEA/H/C/002549

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Krka d.d., Novo mesto submitted on 25 April 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Tolucombi, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 April 2011.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Treatment of essential hypertension.
Tolucombi fixed dose combination (40 mg telmisartan/12.5 mg hydrochlorothiazide) is indicated in adults whose blood pressure is not adequately controlled on telmisartan alone.
Tolucombi fixed dose combination (80 mg telmisartan/12.5 mg hydrochlorothiazide) is indicated in adults whose blood pressure is not adequately controlled on telmisartan alone.
Tolucombi fixed dose combination (80 mg telmisartan/25 mg hydrochlorothiazide) is indicated in adults whose blood pressure is not adequately controlled on Tolucombi 80 mg/12.5 mg (80 mg telmisartan/12.5 mg hydrochlorothiazide) or adults who have been previously stabilised on telmisartan and hydrochlorothiazide given separately.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product MicardisPlus 80mg/ 25 mg tablets (highest dose) instead of non-clinical and clinical unless justified otherwise.

Information on paediatric requirements

Not applicable

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:

Product name, strength, pharmaceutical form: MicardisPlus 40 mg/12.5 mg, 80 mg/12.5 mg, 80mg/ 25 mg tablets

- Marketing authorisation holder: Boehringer Ingelheim International GmbH
- Date of authorisation: 2002-04-19
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number: : EU/1/02/213/001-023

- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

Product name, strength, pharmaceutical form: MicardisPlus 40 mg/12.5 mg, 80 mg/12.5 mg, 80mg/ 25 mg tablets

- Marketing authorisation holder: Boehringer Ingelheim International GmbH
- Date of authorisation: 2002-04-19
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number:EU/1/02/213/001-023

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: MicardisPlus 80mg/25mg tablets
- Marketing authorisation holder: Boehringer Ingelheim International GmbH
- Date of authorisation: 2002-04-19
- Marketing authorisation granted by:
  - Community
  - Member State (EEA) : Germany
  - (Community) Marketing authorisation number(s): EU/1/02/213/017-023
  - Bioavailability study number(s): Krka study code: 10-302

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP and the evaluation team were:

Rapporteur: Alar Irs

- The application was received by the EMA on 25 April 2012.
- The procedure started on 23 May 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 August 2012 (Annex 1).
- During the meeting on 20 September 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 September 2012 (Annex 2).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 12 October 2012.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 23 November 2012 (Annex 3).
- During the CHMP meeting on 13 December 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant (Annex 4).

- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 17 December 2012.
- During the meeting on 17 January 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Tolucombi.

2. Scientific discussion

2.1. Introduction

Tolucombi 40 mg/12.5 mg, 80 mg/12.5 mg and 80 mg/25 mg tablets is a generic medicinal product of MicardisPlus, which has been authorised in the EU since 19 April 2002.

Tolucombi is a fixed-dose combination of the active substances telmisartan, a non-peptide angiotensin II receptor (type AT_1) antagonist, and hydrochlorothiazide, a thiazides diuretic. Telmisartan acts as vasodilator and reduces peripheral resistance. It is given in the management of hypertension, heart failure, myocardial infarction and nephropathy. Thiazides such as hydrochlorothiazide (HCTZ) are used in the treatment of hypertension and heart failure.

Telmisartan /hydrochlorothiazide tablets are administered orally for treatment of hypertension. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone. The effects of fixed dose combination of telmisartan/HCTZ on mortality and cardiovascular morbidity are currently unknown.

The safety and efficacy profile of telmisartan and hydrochlorothiazide has been demonstrated in several clinical trials details of which can be found in the EPAR of MicardisPlus. In addition, there is a long-term post-marketing experience contributing to the knowledge of the clinical use of this product. Since this application is a generic application referring to the reference medicinal product MicardisPlus, summary of the clinical data of telmisartan and hydrochlorothiazide is available and no new clinical studies regarding pharmacology, pharmacokinetics and efficacy and safety have been conducted.

The approved indication is:

Treatment of essential hypertension.

Tolucombi fixed dose combination (40 mg telmisartan/12.5 mg hydrochlorothiazide) is indicated in patients whose blood pressure is not adequately controlled on telmisartan alone.

Tolucombi fixed dose combination (80 mg telmisartan/12.5 mg hydrochlorothiazide) is indicated in patients whose blood pressure is not adequately controlled on telmisartan alone.

Tolucombi fixed dose combination (80 mg telmisartan/25 mg hydrochlorothiazide) is indicated in patients whose blood pressure is not adequately controlled on Tolucombi 80 mg/12.5 mg (80 mg telmisartan/12.5 mg hydrochlorothiazide) or adults who have been previously stabilised on telmisartan and hydrochlorothiazide given separately.

The indication proposed for Tolucombi is the same as authorized for the Reference medicinal product.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as tablets containing 40 mg/12.5 mg, 80 mg/12.5 mg and 80 mg/25 mg of telmisartan and hydrochlorothiazide as active substances. The composition is described in section 6.1 of the SmPC.

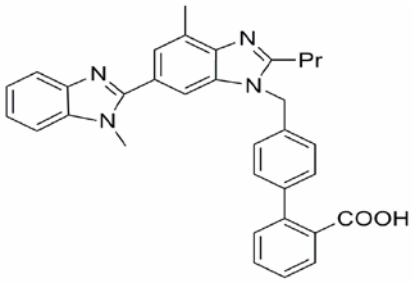
Telmisartan/HCTZ 40/12.5 mg tablets are white to almost white or pinkish white on one side and pink marbled on the opposite side of two-layer biconvex oval tablet.
Telmisartan/HCTZ 80/12.5 mg tablets are white to almost white or pinkish white on one side and pink marbled on the opposite side of two-layer biconvex oval tablet.
Telmisartan/HCTZ 80/25 mg tablets are white to yellowish white on one side and yellow marbled on the opposite side of two-layer, biconvex, oval tablet.

The product is packed in two different blister packs: OPA/Al/PVC foil//Al foil blisters and OPA/Al/PE+DES foil//Al foil blisters.

2.2.2. Active substance

Telmisartan

Telmisartan is a white to off-white crystalline powder, slightly hygroscopic, practically insoluble in water, slightly soluble in methanol, sparingly soluble in methylene chloride and freely soluble in organic solvents. The chemical name is 4'-[[4-Methyl-6-(1-methyl-1H-benzimidazol-2-yl)-2-propyl-1Hbenzimidazol-1-yl] methyl]biphenyl-2-carboxylic acid, and the structural formula as follows:



Telmisartan has no chiral centres and exhibits no stereoisomerism. The active substance exhibits polymorphism.

Telmisartan is subject of an European Pharmacopoeia monograph.

Manufacture

The active substance is supplied by two different sources. Supplier A has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for telmisartan which has been provided within the current Marketing Authorisation Application. The relevant information has been assessed by EDQM.

Supplier B resorts to two synthetic processes. Adequate in-process controls are applied during the synthesis with both processes. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Detailed information on the manufacturing of the active substance has been provided and it was considered satisfactory.

Specification

Supplier AThe active substance will be tested and assessed by the finished product manufacturer applying the methods and specifications laid down in the Ph. Eur. monograph and CEP of telmisartan.

Satisfactory batch analysis data were provided demonstrating that the active ingredient can be manufactured reproducibly.

All compendial and in-house test methods are adequately validated.

Supplier BThe active substance specification is inline with the Ph.Eur. monograph and includes tests for appearance, identification (IR), appearance of solution, related substances (HPLC), assay (HPLC), residual solvents (GC), loss on drying, and sulphated ash.

Batch analysis data were provided for representative batches produced with the proposed two synthetic routes, and the batch analysis data show that the active ingredient can be manufactured reproducibly.

All compendial and in-house test methods are adequately validated.

Stability

Supplier AIn the CEP the re-test period of the substance is 3 years if stored in double LDPE bags, placed in a HDPE drum is stated.

Supplier BThe active substance is packaged in previously prepared cartons containing primary transparent LDPE bag in secondary Al-TX bag. The primary bag is closed with a plastic clip and the secondary bag is closed by the thermo sealing.

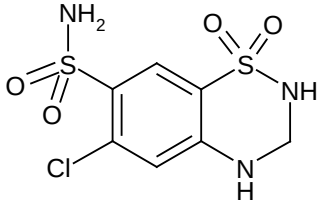
Batch data of active substance (from process 1 and 2) packed in a container closure system similar to the intended commercial packaging were put on stability testing as per ICH conditions: under long term (25°C/60%RH) for up to 36 months, and accelerated (40°C/75%RH) for up to 6 months. Satisfactory results on stress conditions (e.g. photostability, acid, hydrolysis and oxidation) were also provided.

The following parameters were tested: description, identification, water content, related substances and assay.

The stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 3 years in the proposed container closure system in order to protect from light.

Hydrochlorothiazide

Hydrochlorothiazide (HCT) is a white or almost white crystalline powder, very slightly soluble in water, sparingly soluble in Ethanol and Methanol, soluble in Acetone. Freely soluble in N,N-Dimethylformamide, in n-Butylamine and in diluted solutions of alkali hydroxides. The chemical name is: 6-Chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, and has the following structural formula:



HCT does not show optical activity or different potential isomers. It shows polymorphism; the manufacturer consistently produces the same polymorphic form.

Manufacture

The supplier of HCT has been granted a CEP which has been provided within the current Marketing Authorisation Application. The relevant information has been assessed by EDQM.

Specification

The active substance will be tested and assessed by the finished product manufacturer applying the methods and specifications laid down in the Ph. Eur. monograph and CEP of hydrochlorothiazide. In addition, the finished product manufacturer performs a test for particle size distribution.

Satisfactory batch analysis data were provided demonstrating that the active ingredient can be manufactured reproducibly.

All compendial and in-house test methods are adequately validated.

Stability

In the CEP the re-test period of the substance is 5 years if stored in double PE bags placed in a HMHDPE drum is stated.

2.2.3. Finished medicinal product

Pharmaceutical development

The aim of the studies was to develop a generic, bioavailable and stable tablet dosage form of telmisartan and hydrochlorothiazide. Telmisartan/Hydrochlorothiazide 40/12.5 mg, 80/12.5 mg and 80/25 mg tablets developed by Krka are two layer tablets essentially similar to MicardisPlus 40/12.5 mg, 80/12.5 mg and 80/25 mg tablets, the innovator product from Boehringer Ingelheim. The development process started with strength 80/25 mg and was focused on the dosage form, where telmisartan and hydrochlorothiazide are physically separated to avoid compatibility issues of telmisartan and hydrochlorothiazide.

All excipients are well known pharmaceutical ingredients and their quality is compliant with compendial standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The discriminatory power of the dissolution method has been demonstrated. Satisfactory dissolution data and comparative dissolution studies are provided for both substances.

There are two different immediate packaging: laminated OPA/Al/PVC foil in combination with aluminium foil and laminated OPA/Al/PE foil with desiccant in combination with aluminium foil. The suitability and compatibility of the chosen packaging material with the bulk tablets, and the compatibility of excipients with drug substance is confirmed by performed stability studies.

Adventitious agents

Statements from producers confirming that the excipients are BSE/TSE free are submitted.

Manufacture of the product

All three strengths, 40/12.5 mg tablets, 80/12.5 mg tablets and 80/25 mg tablets are manufactured by a standard manufacturing process according to the same manufacturing steps.

The manufacturing process has been adequately described and the critical steps have been identified. In process controls are adequate for this tablet preparation.

The validation protocol proposed for the full scale batches has been provided and the quality of the production batches will be evaluated through the results of in process testing as well as the results of finished product testing.

The batch analysis data of each strength shows that the tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

Product specification

The finished product release specifications include appropriate tests for appearance, identification (HPLC and TLC), assay (HPLC), uniformity of dosage units, dissolution, degradation products (HPLC) and microbial quality.

All analytical procedures and test methods have been adequately described and the validation data presented is acceptable.

Batch analysis results confirm consistency and uniformity of manufacture and indicate that the process is capable and under control.

Stability of the product

Stability data of batches stored in a container closure systems equivalent to those proposed for marketing were provided under long term conditions for up to 12 months (25 ºC/60 % RH) and for up to 6 months under accelerate conditions (40 ºC/75 % RH), in line with ICH guidelines.

Samples were tested for appearance, related substances, assay, dissolution and microbiological quality.

Photostability studies were conducted and indicate that drug product is sensitive to light.

All investigated parameters remain within specified limits. The stability studies provided support the shelf-life of 2 years under the storage conditions declared in the SmPC.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non- clinical aspects

2.3.1. Introduction

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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity / environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Tolucombi manufactured by Krka d.d., Novo mesto is considered unlikely to result in any significant increase in the combined sales volumes for all telmisartan/hydrochlorothiazide containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Discussion on Non-Clinical aspects

The CHMP agreed that no further non-clinical studies are required. The ERA is expected to be similar and not increased.

2.3.4. Conclusion on the non-clinical aspects

The CHMP agreed that no further non-clinical studies are required. The ERA is expected to be similar and not increased.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for tablets containing telmisartan/hydrochlorothiazide. To support the marketing authorisation application the applicant conducted a bioequivalence study with the highest strength telmisartan/HCTZ 80/25 mg under fasting conditions. This study was the pivotal study for the assessment.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of telmisartan/HCTZ based on published literature.The SmPC is in line with the SmPC of the reference product.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1 in its current version is of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

The applicant claims biowaiver for telmisartan/HCTZ 40/12.5 mg and 80/12.5 mg strengths. According to the SmPC of the reference product MicardisPlus, the pharmacokinetics of telmisartan is non-linear with more than dose proportional increase in Cmax and AUC. As per literature references submitted by the applicant, the pharmacokinetics of HCTZ is linear over the dose range of 12.5 mg to 25 mg. According to the SmPC, the reference product can be taken with and without food.

Therefore, choice of strength, the highest telmisartan/HCTZ 80/25 mg tablets, and design of the study, a single dose crossover bioequivalence study under fasting condition, are appropriate and in line with the CHMP Guideline on the Investigation of Bioequivalence.

Clinical studies

To support the application, the applicant has submitted a bioequivalence study:
Single dose crossover comparative bioavailability study of telmisartan/hydrochlorothiazide 80 mg / 25 mg tablets in healthy male volunteers under fasting conditions.

2.4.2. Pharmacokinetics

Methods

Study design

Single centre, randomized, single dose, laboratory-blinded, 2-period, 2-sequence, crossover study was conducted to compare the relative bioavailability and therefore the bioequivalence of two different formulations of telmisartan / HCTZ after a single oral dose administration under fasting conditions.

Test and reference products

Test Product:

Name: Telmisartan / hydrochlorothiazide

Dosage form/Route of administration: Tablet / Oral

Regimen: Single dose of 1 x 80 mg/25 mg

Batch size: 100 000 tablets

Manufacturer: KRKA, d.d., Novo Mesto, Slovenia

Reference Product:

Name: MicardisPlus

Dosage form/Route of administration: Tablet / Oral

Regimen: Single dose of 1 x 80 mg/25 mg

Manufacturer: Boeringher Ingelheim Pharma GmbH & Co.KG, Germany

Population(s) studied

The study was conducted in 70 healthy male subjects (volunteers) with a mean age of 36 years (range 19-50 years).

Thirty-nine (39) blood samples were collected on twenty-three (23) occasions as follows:

• For telmisartan (21 samples), blood samples were collected prior to and 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 16, 24, 36, 48 and 72 hours after drug administration.

• For hydrochlorothiazide (18 samples), blood samples were collected prior to and 0.33, 0.67, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 9, 12, 16, 24 and 36 hours after drug administration.

After a, overnight fast, a single dose of the assigned formulation was orally administered in the morning with approximately 240 mL of water. The wash-out period between study periods was of 14 calendar days.

Of the 70 healthy male subjects who were included in the study, 64 subjects completed the crossover design and received a single oral dose of the assigned formulation on day 1 and day 15. Three subjects withdrew their consent on personal reasons before period 2, one subject before period 2 due to upper respiratory tract infection, one subject was withdrawn since he missed three last blood samples in period 1, one subject was withdrawn due to vomiting event in period 1.

Analytical methods

The experimental samples were assayed for telmisartan at the analytical facility of the CROoutside EU using a validated HPLC method with MS/MS detection. The subject sample analysis was performed between 2011/02/25 and 2011/04/18, including re-assays and incurred samples.

The experimental samples were assayed for HCTZ in plasma at the analytical facility of the CRO outside EU using a validated HPLC method with MS/MS detection. The subject sample analysis was performed between 2011/03/01 and 2011/04/19.

Analytical methods were appropriately validated and met the criteria in the EMA Guideline on Bioanalytical Method Validation.

Pharmacokinetic variables

The pharmacokinetic parameters were Cmax, Tmax, AUCT, AUC∞, AUCT/∞, Kel and T½el, which were measured and calculated from the collected blood samples for telmisartan and HCTZ. The main PK parameters were estimated using a non-compartmental approach with a log-linear terminal phase assumption. The trapezoidal rule was used to estimate the area under the curve and the terminal phase was estimated by maximizing the coefficient of determination estimated from the log-linear regression model. The natural logarithmic transformation of Cmax, AUCT and AUC∞ as well as the rank-transformation of Tmax were used for all statistical analysis.

Statistical methods

Statistical analysis was based on a parametric ANOVA model of the pharmacokinetic parameters; two-sided 90% confidence interval of the ratio of geometric means for the Cmax, AUCT and AUC∞ based on ln-transformed data. ANOVA model included sequence, period, treatment, subject (nested within sequence) as fixed effects. Statistical and pharmacokinetic analyses were generated using Kinetic, version 9.01.

Standard non-compartmental pharmacokinetic and statistical analysis using ANOVA and GLM procedure were used and are in line with the EMA guideline on the Investigation of Bioequivalence.

Results

Of the 70 healthy subjects who were included in the study, 64 subjects completed the crossover design and were included in the PK and statistical analysis. The main results obtained from the BE study are summarised in Tables 1,2,3, and 4 below.

Table 1. Summary of Main Study Results – Telmisartan.

PARAMETER	TEST		REFERENCE	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (ng/mL)	271.69	72.5	264.24	69.6
ln (C_{max})	5.3863	12.6	5.3412	13.4
T_{max} (hours) *	0.92	57.5	0.83	55.8
AUC_T (ng·h/mL)	1834.88	85.3	1796.12	89.6
ln (AUC_T)	7.2553	10.0	7.2037	10.7
AUC_∞ (ng·h/mL)	2230.96	85.5	2149.22	90.8
ln (AUC_∞)	7.4676	9.1	7.3996	10.0
$AUC_{T/\infty}$ (%)	90.73	6.4	92.03	5.8
K_{el} ($hours^{-1}$)	0.0345	30.9	0.0390	34.3
$T_{½el}$ (hours)	22.21	37.4	20.28	40.6

* For T_{max}, the median is presented.

Table 2. Comparison of Results with Standards for Bioequivalence – Telmisartan

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	31.1	219.34	209.60	104.65	95.66	114.48
AUC_T	12.9	1415.95	1349.32	104.94	101.03	109.00

* units are ng/mL for C_{max} and ng·h/mL for AUC_T

Table 3. Summary of Main Study Results – Hydrochlorothiazide

PARAMETER	TEST		REFERENCE	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (ng/mL)	161.77	24.9	168.32	28.5
ln (C_{max})	5.0570	4.8	5.0878	5.4
T_{max} (hours) *	1.50	35.2	1.50	38.1
AUC_T (ng·h/mL)	1068.71	20.4	1048.66	22.5
ln (AUC_T)	6.9534	3.0	6.9302	3.3
AUC_∞ (ng·h/mL)	1144.61	21.8	1122.58	23.7
ln (AUC_∞)	7.0198	3.1	6.9962	3.4
$AUC_{T/\infty}$ (%)	93.60	2.5	93.68	3.5
K_{el} ($hours^{-1}$)	0.0684	13.2	0.0691	16.1
$T_{½el}$ (hours)	10.31	13.2	10.35	20.1

* For T_{max}, the median is presented.

Table 4. Comparison of Results with Standards for Bioequivalence – Hydrochlorothiazide

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	17.9	157.41	162.79	96.69	91.75	101.91
AUC_T	8.3	1049.61	1025.96	102.30	99.84	104.83

* units are ng/mL for C_{max} and ng·h/mL for AUC_T

The test to reference product ratio of geometric LS means and corresponding 90% confidence interval for the Cmax and AUCT were within the acceptance range of 80.00 to 125.00% for both telmisartan and HCTZ. Therefore, based on telmisartan and HCTZ, the test formulation (Telmisartan/HCTZ 80 mg/25 mg tablets, KRKA, d.d., Novo mesto, Slovenia) is considered by the CHMP to be bioequivalent to the reference formulation (MicardisPlus 80 mg/25 mg tablets, Boehringer Ingelheim Pharma GmbH & Co.KG, Germany) under fasting conditions.

Biowaiver

The applicant claims for a biowaiver for telmisartan/HCTZ 40/12.5 mg and 80/12.5 mg strengths. The data submitted to support the biowaiver claim are acceptable All criteria needed for a biowaiver claim are also fulfilled and accepted by the CHMP.

Safety data

In the BE study 70 adverse events were reported by 41 subjects out of 70. No serious adverse events (AEs) or deaths were reported during this study and no subjects were withdrawn from the study for safety reasons. Overall, the drugs tested were generally safe and well tolerated by subjects included in this study.

Conclusions

Bioequivalence between the Telmisartan/HCTZ KRKA 80/25 mg tablets and the reference product MicardisPlus 80/25 mg tablets have been demonstrated. Bioequivalence studies with additional Telmisartan/HCTZ KRKA 40/12.5 mg tablets and Telmisartan/HCTZ KRKA 80/12.5 mg tablets can be waived.

Based on the presented bioequivalence study Tolucombi is considered bioequivalent with MicardisPlus.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

This application concerns a generic medicinal product Telmisartan/HCTZ KRKA 40/12.5 mg tablets, Telmisartan/HCTZ KRKA 80/12.5 mg tablets and Telmisartan/HCTZ KRKA 80/25 mg tablets. A single dose 2-period crossover bioequivalence study under fasting conditions was conducted with the highest telmisartan/HCTZ 80/25 mg strength. Design of the study was appropriate, the reference product MicardisPlus (Boerhinger Ingelheim GmbH, Germany) can be taken with and without food. Selection of the highest strength is appropriate since according to the SmPC of the reference product, telmisartan has non-linear PK with more than dose proportional increase in AUC. As per submitted literature references, PK of HCTZ is linear over the dose range of 12.5 mg to 25 mg. Clinical site of the study has been regularly inspected by regulatory authorities. Study report contained all relevant sections and annexes. Blood sample collection time was sufficient, no pre-dose samples contained detectable levels of investigational drugs. The conduct of the study was in line with the CHMP Guideline on the Investigation of Bioequivalence. For the highest 80/25 mg strength bioequivalence between the generic and the EU reference product MicardisPlus has been demonstrated both for the Cmax (telmisartan 104.65 [90%CI 95.66; 114.48]; HCTZ 96.69 [90%CI 91.75; 101.91]) and AUCT (telmisartan 104.94 [90% CI 101.03; 109.00]; HCTZ 102.30 [99.84 ; 104.83]).

A biowaiver claim has been submitted for additional Telmisartan/HCTZ KRKA 40/12.5 mg and Telmisartan/HCTZ KRKA 80/12.5 mg tablets. All criteria for a biowaiver according to the CHMP Guideline on the Investigation of Bioequivalence were fulfilled.

2.4.6. Conclusions on clinical aspects

The CHMP concluded that the generic telmisartan/HCTZ KRKA 40/12.5 mg tablets, telmisartan/HCTZ KRKA 80/12.5 mg tablets and telmisartan/HCTZ KRKA 80/25 mg tablets are bioequivalent with the reference product MicardisPlus (Boerhinger Ingelheim GmbH, Germany).

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk management plan

The applicant submitted a risk management plan.

Table 1. Summary of the risk management plan

Safety concern	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
Important identified risks		
Sepsis	Routine pharmacovigilance activities	Routine risk minimisation activities
Renal dysfunction as consequence of dual RAAS blockade	Routine pharmacovigilance activities	Routine risk minimisation activities
Foetotoxicity	Routine pharmacovigilance activities	Routine risk minimisation activities
Hypoglycaemia	Routine pharmacovigilance activities	Routine risk minimisation activities
Important potential risks		
Increase in hepatic-related adverse reactions in the Japanese population	Routine pharmacovigilance activities	Routine risk minimisation activities
Rhabdomyolysis	Routine pharmacovigilance activities	Routine risk minimisation activities
Interstitial lung diseases	Routine pharmacovigilance activities	Routine risk minimisation activities
Severe cutaneous	Routine pharmacovigilance activities	Routine risk minimisation

reactions		activities
Suicide/self-injury	Routine pharmacovigilance activities	Routine risk minimisation activities
Malignancies	Routine pharmacovigilance activities	Routine pharmacovigilance activities
Important missing information	Not applicable	Not applicable

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

PSUR submission

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This is an application for a generic medicinal product containing of telmisartan/ hydrochlorothiazide tablets. The reference product, MicardisPlus, is indicated for treatment of essential hypertension (40 mg telmisartan/12.5 mg hydrochlorothiazide is indicated in adults whose blood pressure is not adequately controlled on telmisartan alone; 80 mg telmisartan/12.5 mg hydrochlorothiazide is indicated in adults whose blood pressure is not adequately controlled on telmisartan alone; 80 mg telmisartan/25 mg hydrochlorothiazide is indicated in adults whose blood pressure is not adequately controlled on 80 mg telmisartan/12.5 mg hydrochlorothiazide or adults who have been previously stabilised on telmisartan and hydrochlorothiazide given separately).

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient.

From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study constitutes pivotal basis with a single dose crossover comparative bioavailability study of 80 mg telmisartan/ 25 mg hydrochlorothiazide tablets in healthy male volunteers in fasting state. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. The choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Tolucombi 80 mg telmisartan/ 25 mg hydrochlorothiazide tablets met the protocol-defined criteria for bioequivalence when compared with the MicardisPlus. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-∞, and Cmax for both active substances were all contained within the protocol-defined acceptance range of 80.00 to 125.00 %. Bioequivalence of the two formulations was demonstrated.

The applicant claimed for a biowaiver for telmisartan/ hydrochlorothiazide 40/12.5 mg and 80/12.5 mg strengths. All criteria needed for the requested biowaiver claim are fulfilled.

A benefit/risk ratio comparable to the reference product can therefore be concluded as positive.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Tolucombi in the treatment of treatment of essential hypertension; Tolucombi fixed dose combination (40 mg telmisartan/12.5 mg hydrochlorothiazide) is indicated in adults whose blood pressure is not adequately controlled on telmisartan alone; Tolucombi fixed dose combination (80 mg telmisartan/12.5 mg hydrochlorothiazide) is indicated in adults whose blood pressure is not adequately controlled on telmisartan alone; Tolucombi fixed dose combination (80 mg telmisartan/25 mg hydrochlorothiazide) is indicated in adults whose blood pressure is not adequately controlled on Tolucombi 80 mg/12.5 mg (80 mg telmisartan/12.5 mg hydrochlorothiazide) or adults who have been previously stabilised on telmisartan and hydrochlorothiazide given separately, is favourable and therefore recommends the granting of the marketing authorisation.

Conditions or restrictions regarding supply and use

Medicinal Product subject to prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP shall be submitted annually until renewal.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the member states

Not applicable