EMA/342695/2010

Evaluation of Medicines for Human Use

Assessment report

Tolura

International Nonproprietary Name: telmisartan

Procedure No. EMEA/H/C/001196

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 03 July 2009 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Tolura, in accordance with the centralised procedure falling within the scope of the Annex to Regulation (EC) 726/2004 under Article 3 (3) – 'Generic of a Centrally authorised product'.

The legal basis for this application refers to:

A - Centralised / Article 10(1) / Generic application of Directive 2001/83/EC.

The chosen reference product is:

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

- Product name, strength, pharmaceutical form: Micardis 20 mg, 40 mg, 80 mg tablets
- Marketing authorisation holder: Boehringer Ingelheim International GmbH
- Date of authorisation: (dd-mm-yyyy) 16th December 1998
- Marketing authorisation granted by:
  - Community
- Community Marketing Authorisation number(s): EU/1/98/090/001-020

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: Micardis 80 mg tablets
- Marketing authorisation holder: Boehringer Ingelheim International GmbH
- Date of authorisation: (dd-mm-yyyy) 16th December 1998
- Marketing authorisation granted by:
  - Community
- Community Marketing Authorisation number(s): EU/1/98/090/005-008, 014, 016, 018, 020
- Member State of source: Germany
- Bioavailability study reference number: 08-221

1.1.1. Licensing status:

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

The Rapporteur appointed by the CHMP was János Borvendég.

1.2. Steps taken for the assessment of the product

- The application was received by the Agency on 3 July 2009.
- The procedure started on 22 July 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 October 2009.
- During the meeting on 16-19 November 2009, 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 19 November 2009.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 December 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 January 2010.
- During the CHMP meeting on 15-18 February 2010, the CHMP agreed on a List of Outstanding Issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 24 February 2010.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the CHMP List of Outstanding Issues to all CHMP members on 3 March 2010.
- During the meeting on 15-18 March 20010, 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 Tolura on 18 March 2010.
- The CHMP opinions were forwarded in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 4 June 2010.

2. Scientific discussion

2.1. Introduction

Tolura is indicated for the treatment of essential hypertension in adults. Telmisartan active substance is an orally active and specific angiotensin II receptor (type AT1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. The active substance selectively binds the AT1 receptor and does not exhibit any partial agonist activity at the AT1 receptor. The binding is long-lasting. It does not show affinity for other receptors, including AT2 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, neither inhibits angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore it is not expected to potentiate bradykinin-mediated adverse effects.
Tolura 20 mg, 40 mg and 80 mg tablets are generic of the centrally authorised Micardis 20 mg, 40 mg and 80 mg tablets.
The efficacy and safety of telmisartan has been demonstrated in several well-controlled studies. A summary of these studies can be found in the EPAR of the reference product Micardis.
The reference product was authorized in the Community on 16th December 1998 for Boehringer Ingelheim International GmbH. Bioequivalence to the reference product from the German market was demonstrated at the highest strength. Regarding the lower strengths of Tolura a biowaiver has been accepted since all the requirements as per Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled.

The indication proposed for Tolura is different from the reference medicinal product. It is part of the indication approved for the reference medicinal product.
The therapeutic indication of Tolura is:
Treatment of essential hypertension in adults.

The therapeutic indication of Micardis is:
Treatment of essential hypertension in adults.
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.

2.2. Quality aspects

2.2.1. Introduction

Tolura is presented as immediate release tablets, containing 20, 40 and 80mg of telmisartan as the active substance.
Other ingredients are defined in the SPC section 6.1. All strengths have the same proportional composition.
The tablets are packaged in OPA/Alu/PVC/Alu blister packs.

2.2.2. Active substance

The active substance of Tolura is telmisartan, which has the chemical name: 2-(4-{[4-methyl-6-(1-methyl-1*H*-1,3-benzodiazol-2-yl)-2-propyl-1*H*-1,3-benzodiazol-1-yl]methyl}phenyl)benzoic acid. It corresponds to the molecular formula $C_{33}H_{30}N_4O_2$ and relative molecular mass of 514.6. It appears as White to slightly yellowish crystalline powder, practically insoluble to water, and slightly soluble to methanol.
Its pKa has been measured 4.45 ± 0.09 and the logP: 7.7
Two different crystalline forms denoted as Form A and Form B are described in the literature. Krka is using one of these crystalline forms, however, this characteristic is not of relevance in drug product manufacturing process.

2.2.2.1. Manufacture

The active substance is supplied by two manufacturers. For one of them a Certificate of Suitability (CEP) granted by the EDQM has been presented covering the manufacturing.
The manufacturing process employed by the other active substance manufacturer comprised of a number of synthetic, crystallisation and purification steps. Specifications of starting materials, reagents and solvents used were provided. Critical steps and in-process controls have been properly defined and sufficiently described.

2.2.2.2. Specification

Telmisartan is described in the European Pharmacopoeia (Ph. Eur). The specification of the active substance as set up by the drug product manufacturer includes tests and limits for appearance (visual), solubility (Ph.Eur.), identification (IR), appearance of solution (Ph.Eur.), related substances (HPLC), loss on drying (Ph.Eur.), sulphated ash (Ph.Eur.), assay (Ph.Eur.) and residual solvents (GC).
Except for residual solvents, all the tests are performed according to the procedures described in Ph.Eur. monograph for telmisartan and Ph.Eur. general procedures. Additional testing methods and limits have been included for the XRD pattern from the first manufacturer and for a specific process related impurity from the second manufacturer. The batch analysis results showed that the contents of this additional impurity in all tested batches are comparable and are below the limit of identification set in accordance with ICHQ3A Guideline on Impurities and Ph.Eur. general monograph.
Analytical test results of three batches of telmisartan from the first manufacturer and five from the second were provided. Batch sizes, manufacturing sites and dates are indicated. All the results comply with the actual specification. The results confirm batch to batch consistency and uniformity of the quality of the substance and indicate that the process is under control.

2.2.2.3. Stability

The CEP provided by one of the manufacturers covers the re-test period and packaging material.
Three production scale batches manufactured by the second manufacturer have been stored over 12 months under 25°C/60% RH (long term), 6 months under 40°C/75% RH (accelerated) conditions and also for photostability.
After 12 months of storage at long term conditions in packaging representative of those intended for commercial use, all parameters comply with the requirements and no trend was observable. In the accelerated conditions all the results remain within specification and no significant change was observed.

2.2.3. Finished Medicinal Product

2.2.3.1. Pharmaceutical Development

The aim of the development was to obtain an immediate-release tablet containing qualitatively and quantitatively the same drug substance and exhibiting the same bioavailability as the reference product.
Most of development work was performed on one tablet strength. The other two strengths were prepared by proportional decrease or increase of the tablet weight.
In the early stages of the formulation development different types of manufacturing process were tried until optimal process was reached. It has been shown that the particle size of telmisartan is irrelevant and no specification for particle size is set.
In the early stage of development, various dissolution conditions were tested in order to find a discriminative testing method. Dissolution studies were performed on reference product and Tolura tablets in different dissolution media in physiological pH range (pH 1 – pH 6.8). The similarity factors (f2) in all tested media are higher than 50 therefore dissolution profiles can be considered similar supporting the biowaiver for the two lower strengths. Another study demonstrated the discriminative nature of the selected dissolution method.
The impurity profiles of Tolura tablets and of the reference product are considered similar.
Tolura is packaged in blister packs consisting of OPA/Al/PVC film and aluminium foil.

2.2.3.2. Adventitious agents

Tolura tablets contain lactose monohydrate. Supplier of lactose monohydrate provided confirmations regarding TSE/BSE risk.

2.2.3.3. Manufacture of the product

The manufacturing process is considered as a standard process which includes the following main steps: granulation, mixing, tabletting and packaging. The product is manufactured in two sites.
Based on the obtained results during the process development and manufacture of the dosage form the critical steps have been identified and appropriate in-process controls have been set up. Validation protocol for the production batches, valid for all production sites has been provided. Concurrent process validation will be performed on three consecutive commercial batches.

2.2.3.4. Product specification

The release and shelf life specification of Tolura includes tests and limits for appearance (visually), identification of drug substance (HPLC, TLC, only at release), uniformity of dosage units (Ph.Eur.), disintegration (Ph.Eur.), related substances (HPLC), dissolution (UV, Ph.Eur.), assay (HPLC), and microbiological contamination (Ph.Eur.- non routinely).
Batch analysis data of two batches of each of strength from both sites were presented. All the presented results were within the specification limits and confirm both the consistency of production and good performance of the analysis methods. It can be concluded that the analytical tests are suitable, manufacturing process and analysis are well controlled.

2.2.3.5. Stability of the product

Two pilot batches of each strength were put on long-term (25±2°C/60±5%RH) and accelerated (40±2°C/75±5%RH) stability testing conditions packaged in the material proposed for the marketed product.

Photostability test was performed according to the ICH Guideline Q1B on one batch of each strength.
Results of stability tests of batches stored at long-term for up to 12 months as well as at accelerated conditions for six months showed no significant changes in the chemical and physical properties investigated.
Slight change in colour of the tablets was observed after photostability test. All other parameters comply with the prescribed specifications after photostability test.
Based on the stability data presented the proposed shelf life and storage conditions can be accepted for Tolura.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory 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.

2.3. Non-clinical aspects

Telmisartan is a widely used well-known active substance. Its pharmacodynamic, pharmacokinetic and toxicological properties are well characterised and new non-clinical studies were not provided. No further studies are required and the applicant has justified why no such data was provided.

The non-clinical overview provided was based on a literature review, which is considered appropriate.

All excipients and other ingredients are approved products used within recommended limits. However, Tolura contains lactose while the reference product Micardis does not. Lactose is a well-known excipient but this change might be of importance to patients with lactose intolerance.

Introduction of the product on the market is unlikely to result in any significant increase in the combined sales volumes for all telmisartan products, and would thus not be expected to have an adverse effect on the environment. Taking this into account and on the basis of the CHMP Guideline on Environmental Risk Assessment of Medicinal Products for Human Use (CPMP/SWP/4447/00), a formal environmental risk assessment is not considered necessary.

2.4. Clinical aspects

2.4.1. Introduction

The CHMP assessment addressed pharmacokinetic data in respect of one bioequivalence study.

2.4.2. GCP

The applicant has provided a statement that the bioequivalence study was performed in accordance with GCP and the ethical requirements of Directive 2001/20. The clinical, analytical and statistical parts of the study were performed by Clinical Research Organisation (CRO) in Canada, which has been inspected by different EU regulatory agencies and also by FDA, ANVISA and HPFB of Canada. Following these inspections CRO was found to be compliant with the regulatory requirements

2.4.3. Pharmacokinetics

Study 08-221

- Methods

The bioequivalence study with Telmisartan 80 mg tablets (Study 08-221) was a single-dose, randomized, two-way cross-over study conducted under fasting conditions with a 2 week washout period between the doses. The test product (Telmisartan 80 mg tablets, manufactured by KRKA) was compared with the reference (Micardis 80 mg tablets, manufactured by Boehringer Ingelheim Pharma, Germany).

70 healthy male volunteers were enrolled in the study and 68 completed the study in its entirety. Pharmacokinetic and statistical analyses were performed on the data from all subjects that completed the study in its entirety.

The trial and analysis of the data were complied with Note for Guidance concerning bioavailability and bioequivalence trials (CPMP/QWP/EWP/1401/98).

Study Code: 08-221
Clinical Study Period: 2008/09/08 to 2008/10/23

- Results

PARAMETER	TEST		REFERENCE	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (ng/mL)	195.91	58.9	178.80	56.1
t_{max} (hours)*	1.00	65.0	1.25	63.7
AUC_t (ng-h/mL)	1210.03	67.5	1194.34	74.2
AUC_∞ (ng-h/mL)	1811.89	53.6	1835.12	58.9
AUC_t/ AUC_∞ (%)	84.88	9.4	83.92	9.4

* Median

PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
Cmax	33.5	165.20	152.22	108.53	98.85	119.15
AUC_t	18.2	952.81	896.06	106.33	100.97	111.98
AUC_∞	15.7	1449.72	1442.52	100.50	94.64	106.73

- **Discussion**

This study confirms that the test product (Tolura 80mg tablets) is bioequivalent to the Reference formulation (Micardis 80mg tablets) with respect to rate and extent of availability.

The study was conducted according to Good Clinical and Good Laboratory Practice. The submitted documentation is sufficiently detailed to make a reliable assessment. There is not any sign of misconduct or not following the recommendations of the relevant guidelines.

The design employed was appropriate for bioequivalence studies. A single dose study is considered appropriate in view of the fact that telmisartan does not accumulate during repeated administration. It was a good choice of carrying out the bioequivalence study with the highest strength since telmisartan concentrations increases faster than the dose in the requested dose range (20mg – 80 mg).

The mean AUCt/AUCinf ratios were 84.9% and 83.9 % for the Test and the Reference products, respectively. These values are above the requirements (80%) and they indicate that the sampling period was sufficiently long.

Telmisartan can be considered a highly variable drug because the within-subject variability of Cmax was 33.5%. However the study power was enough to meet the conventional 80%-125% criterion.

The 90% geometric confidence intervals of the ratio (Test/Reference) of least-squares means of the log transformed data were within the internationally accepted range of 80% and 125% for AUC0-t and for Cmax as well.

These results also show that the biowaiver can be granted for the lower strengths because the formulation is proportional and strengths not tested in the bioequivalence study show similar behaviour in the whole range of physiological pH values including pH 1.

No serious adverse events were recorded in 70 subjects during conduct of this trial, while 22 subjects experienced a total of 36 adverse events. 20 adverse events (15 different types) were reported administration of the test product and 21 adverse events (16 different type) were reported after administration of the reference product. 5 adverse events associated with post-trial laboratory test were imputed to both product. 4 possibly related events were unexpected (blood alkaline phosphatase increased, blood bilirubine increased, neutrophil count decreased and libido decreased).

The indication of Tolura is different from that of the reference medicinal product, Micardis (please see section 2.1). Thus, the Product Information has been adequately amended to reflect this change and this is considered acceptable.

- **Conclusions**

Based on the presented bioequivalence study Tolura is considered bioequivalent with Micardis.

2.4.4. Pharmacodynamics

No studies were submitted, which is acceptable.

2.4.5. Post marketing experience

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

2.5. Pharmacovigilance

2.5.1. Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements. The MAH must ensure that the system of pharmacovigilance, as described in version DescPhSys000001/17, is in place and functioning before and whilst the product is on the market.

PSUR cycle

The PSUR submission schedule should follow the PSUR schedule for the reference product Micardis. Thus, the MAH will have to submit PSURs on a yearly basis, unless otherwise specified by the CHMP.

2.5.2. Risk management plan

Not applicable. The application is based on a reference medicinal product for which no safety concerns requiring specific risk minimization activities have been identified.

The present procedure is a generic application. Given the safety profile of the reference product, which is considered well established since it has been on the market for more than 10 years, and the demonstrated bioequivalence between the Tolura tablets and the reference product, the CHMP agrees that no RMP is needed and no risk minimization activities in addition to the recommendations included in the SmPC and Package Leaflet are necessary.

2.5.2.1. User consultation

The criterion for a successful Readability Test was fulfilled. The information presented on user testing of the package leaflet was judged acceptable.

2.6. Conclusions on Clinical aspects

2.6.1. Benefit-risk balance

Telmisartan is a widely used well-known active substance. Its pharmacodynamic, pharmacokinetic and toxicological properties are well characterised and new non-clinical studies were not provided. No further studies are required and the applicant has justified why no such data was provided. The non-clinical overview provided was based on a literature review, which is considered appropriate.

The efficacy, safety and clinical pharmacology of the active ingredient telmisartan are already well-established and documented for the reference product Micardis. The CHMP assessment addressed pharmacokinetic data in respect of one bioequivalence study.

The bioequivalence study confirms that the test product Tolura 80 mg tablets is bioequivalent to the Reference formulation Micardis 80 mg tablets with respect to rate and extent of availability, and is well tolerated. The conclusions of the bioequivalence study conducted with the 80 mg tablets can be extrapolated for the 20mg and 40mg strengths.

There are no new data, which would change the benefit/risk ratio of using telmisartan in general.

The indication proposed for Tolura is different from the reference medicinal product. It is part of the indication approved for the reference medicinal product.
The therapeutic indication of Tolura is:
Treatment of essential hypertension in adults.

2.6.2. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the risk-benefit balance of Tolura in the Treatment of essential hypertension in adults was favourable and therefore recommended the granting of the marketing authorisation.