London, 21 July 2011
EMA/777686/2011
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Telmisartan Teva Pharma

International non proprietary name: telmisartan

Procedure No. EMEA/H/C/002511

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

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Table of contents

List of Abbreviations

AII: Angiotensin II

ACE: Angiotensin Converting Enzyme

ACEI: Angiotensin Converting Enzyme Converting

ASMF: Active Substance Master File

AT1: Angiotensin I

BUN: Blood Urea Nitrogen

CHF: Congestive Heart Failure

CHMP: Committee for Medicinal Products for Human Use

EMA: European medicines agency

GCP: Good Clinical Practice

ERA: Environmental Risk Assessment

MA: Marketing Authorisation

MAH: Marketing authorisation holder

MAP: Mean Arterial Pressure

MTD: Maximum Tolerated Dose

NSAIDs: Non-steroidal Anti-inflammatory Drugs

PRA: Plasma-Renin Activity

RAAS: Renin-Angiotensin-Aldosterone System

SmPC: Summary of product characteristics

1 Background information on the procedure

1.1 Submission of the dossier

The applicant Teva Pharma B.V. submitted on 10 May 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Telmisartan Teva Pharma, 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 17 February 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 in adults.

The legal basis for this application refers to Article 10(1) of Directive 2001/83/EC.

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Micardis.

This application is submitted as a multiple of Telmisartan Teva (EMEA/H/C/001146) authorised on 26 January 2010 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

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: Micardis, 20 mg, tablets
  - Marketing authorisation holder: Boehringer Ingelheim International GmbH
  - Date of authorisation: 16-12-1998
  - Marketing authorisation granted by: Community
    - Community Marketing authorisation number (s): EU/1/98/090/009-012

- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:
  - Product name, strength, pharmaceutical form: Micardis 20 mg, 40 mg and 80 mg tablets
  - Marketing authorisation holder: Boehringer Ingelheim International GmbH
  - Date of authorisation: 16-12-1998
  - Marketing authorisation granted by: Community
    - Community Marketing authorisation number: EU/1/98/090/009-012
      EU/1/98/090/001-004, 013, 015, 017, 019
      EU/1/98/090/005-008, 014, 016, 018, 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: 16-12-1998
- Marketing authorisation granted by: Community
  - Community Marketing authorisation number(s): EU/1/98/090/005-008, 014, 016, 018, 020
- Bioavailability study number(s): Protocol 80019

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

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

The Rapporteur appointed by the CHMP was:

Rapporteur: Prof. János Borvendég

1.2 Steps taken for the assessment of the product

- The application was received by the EMA on 10 May 2011
- The procedure started on 22 May 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 24 June 2011. An updated Assessment Report was circulated on 14 July 2011.
- During the meeting on 18-21 July 2011 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 Telmisartan Teva Pharma on 21 July 2011.

2 Scientific discussion

2.1 Introduction

Telmisartan Teva Pharma 20 mg, 40 mg and 80 mg tablets is a generic medicinal product containing telmisartan as active substance. The reference medicinal product is Micardis 20 mg, 40 mg and 80 mg tablets from Boehringer Ingelheim International GmbH which was centrally authorized on 16 December 1998. The active substance of the reference product is telmisartan.

In addition to the presentations authorised for Micardis, the applicant has added the 30x1, 84x1 and 90x1 presentations for the 20 mg strength, and the 40x1 and 100x1 presentations for the 20 mg, 40 mg and 80 mg strengths.

Telmisartan is indicated for the treatment of essential hypertension in adults. Telmisartan is also indicated for cardiovascular prevention, for the reduction of cardiovascular morbidity in patients with

manifest atherothrombotic cardiovascular disease (history of coronary heart disease, stroke or peripheral arterial disease) or type 2 diabetes mellitus with documented target organ damage.

Telmisartan is an orally active and specific angiotensin II receptor (type AT1) antagonist. It 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. Telmisartan does not exhibit any partial agonist activity at the AT1 receptor. Telmisartan selectively binds the AT1 receptor. The binding is long-lasting. Telmisartan 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. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore it is not expected to potentiate bradykininmediated adverse effects.

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.

Telmisartan Teva Pharma 20 mg, 40 mg and 80 mg tablets is a duplicate of Telmisartan Teva 20 mg, 40 mg and 80 mg tablets (EMEA/H/C/001146), which was granted a valid MA on 26 January 2010. The centrally approved dossier submitted for Telmisartan Teva has been used for this duplicate application, including amendments recently approved through variations. The only differences are the product name and the SmPC and PIL texts.

The indication proposed for Telmisartan Teva Pharma is the same as the authorised indication for Telmisartan Teva (i.e. treatment of essential hypertension). However, due to the patent situation in many EU countries where the combination telmisartan/hydrochlorothiazide is under patent,, the combination telmisartan/hydrochlorothiazide has been deleted from the Telmisartan Teva Pharma SmPC and PIL texts..

2.2 Quality aspects

2.2.1 Introduction

Telmisartan Teva Pharma is presented as immediate release tablets containing telmisartan as active substance. Three strengths have been developed: 20 mg, 40 mg and 80 mg. Other ingredients include microcrystalline cellulose, sodium starch glycolate, poloxamer 188, Lutrol F68, meglumine, povidone (PVP K-30), sorbitol and magnesium stearate. All strengths have the same proportional composition.

The tablets are packaged into Aluminium/Aluminium/Paper (peel push) blisters or Aluminium/Aluminium blisters.

2.2.2 Active Substance

The active substance is telmisartan, a well known active substance described in Ph. Eur. Its chemical name is 4'-[(1,4'-Dimethyl-2'-propyl[2,6'-bi-lH-benzimidazol]-l'-yl)methyl][l,l'-biphenyl]-2-carboxylic acid.

It is a white to slightly yellowish crystalline powder, practically insoluble in water, but freely soluble in organic solvents. Telmisartan has no chiral centers and exhibits no stereoisomerism. The chemical structure of the molecule has been established by spectral (UV, IR, 1H and 13C NMR and mass spectra) elemental and thermal (DSC) analyses. The active substance exhibits polymorphism. The capability of the analytical methods used to discriminate the potential polymorphs has been

demonstrated and batch analysis data confirm that the manufacturing process used consistently produces a single polymorphic form.

Manufacture

Telmisartan is supplied by one manufacturer, and an Active Substance Master File (ASMF) has been submitted. The active substance is synthesised in four main steps using commercially available starting materials. The process is adequately described and satisfactory specifications have been set for reagents, solvents and auxiliary materials used in the process. All critical in-process controls parameters are well established and justified.

Telmisartan active substance is packed into double polyethylene bags which are placed in a triple laminated bag equipped with a silica gel bag, filled with nitrogen, sealed and kept in HDPE containers with a HDPE lid. Specifications and analytical reports for the packaging components have been presented and the suitability of the polyethylene bags for use with food and pharmaceuticals has been confirmed.

Specification

The specification of telmisartan was set to be in line with the current Ph. Eur. monograph and relevant ICH guidelines. The active substance specification includes tests for appearance, assay (HPLC), identification (IR), solubility, appearance of solution, related substances (by HPLC), residual solvents (by GC), X-ray powder diffraction pattern, loss on drying and sulphated ash. In addition, the finished product manufacturer is measuring the particle size distribution.

A reasoned discussion on impurities arising from the starting materials, the route of synthesis and on degradation products has been provided. Impurities A and B are process related impurities and impurities C and D are specified impurities in Ph. Eur. All these impurities are controlled in the final active substance specification in accordance with the Ph. Eur. requirements. The impurity limits are acceptable and there is no concern from the point of view of safety.

The residual solvents are also controlled at release with specifications in accordance with ICH Q3C.

All active substance specifications are considered adequately justified and the non-compendial analytical procedures have been satisfactorily described and validated in accordance with the ICH guidelines.

Batch analysis data from five production scale batches have been provided. The results confirm batch-to-batch consistency and compliance with the Ph. Eur. monograph and the additional specifications.

Stability

Data from stability studies on three production scale batches have been provided. Samples were stored for up to 36 months under long term conditions (25°C/60% RH) and for 6 months under accelerated conditions (40°C/75% RH) in accordance with ICH requirements. All batches have been tested for conformance with the specifications using stability indicating analytical methods. In all cases the batch analysis data met the predefined specifications and no significant changes were observed.

In addition stability data have been provided under stress conditions (heat, acid hydrolysis, base hydrolysis, photo degradation, water hydrolysis and hydrogen peroxide treatment).

Based on the results of the stability studies so far, a valid retest period of 36 months has been justified with no special storage conditions

2.2.3 Finished Medicinal Product

Pharmaceutical Development

The aim of the pharmaceutical development was to obtain immediate-release tablets containing qualitatively and quantitatively the same active substance and exhibiting the same bioavailability as the reference medicinal product, Micardis tablets marketed by Boehringer Ingelheim.

A common formulation was developed for Telmisartan 20 mg, 40 mg and 80 mg tablets that is proportional for each strentgh.

Most of the excipients of Teva's products are common to the reference product except that Micardis tablets do not contain poloxamers (Lutrol F68, Poloxamer 188) and microcrystalline cellulose (Avicel PH-102). All the excipients employed are commonly used in pharmaceutical oral dosage forms and comply with the Ph. Eur.

Further to development studies, wet granulation was chosen as the most appropriate process for the manufacture of the drug product. The manufacturing process is common for all strengths.

The dissolution test design has been extensively discussed and has been found adequate based on data from solubility tests of the active substance and similarity tests for the new and reference products in different pH media. The discriminatory nature of the dissolution method has also been satisfactorily demonstrated.

Adventitious agents

Telmisartan Teva Pharma does not contain excipients from animal or human origin.

Manufacture of the product

The manufacturing process has been sufficiently described. It consists of a standard wet granulation process which includes the following steps: mixing, wet granulation, drying, milling, Sieving, mixing, tabletting and packaging.

All critical process parameters have been identified and controlled by appropriate in-process controls. Validation data from two pilot scale batches of each strength demonstrate that the process is capable, reproducible and provides a product that complies with the in-process and finished product specifications. The validation protocol for the production scale batches had been adequately described.

Telmisartan shows polymorphism. Studies demonstrated that the active substance physical form is consistent between strengths and is stable during the storage of the medicinal product.

Product Specification

The finished product specification includes tests for description, appearance, identification (HPLC, UV), assay (HPLC), dissolution (HPLC), content uniformity (HPLC), friability, thickness, resistance to crushing, impurities and degradation products (HPLC), microbial count and water content.

The finished product specifications are considered appropriate for this dosage form, and they are in general in accordance with current guidelines and European pharmacopoeia.

Batch analysis data from two production scale scaleof batches for each strength have been presented. Batch analysis results comply with the predefined specifications and confirm consistency & uniformity of manufacture and indicate that the process is under control.

Stability of the product

Data from stability studies on two pilot scale batches for each strength have been provided. Samples were stored for up to 12 months under long-term conditions (25°C/60% RH) and for 6 months under accelerated conditions (40°C/75% RH) in accordance with ICH requirements. All batches have been tested for physical (appearance, dissolution), chemical (assay, degradation products) and microbiological parameters using stability indicating methods. In all cases the parameters tested remained within the proposed specifications and no significant changes were observed.

Furthermore, photostability studies have been performed as per ICH Q1B guideline and demonstrate that the film-coated tablets are not sensitive to light.

In conclusion, the stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SmPC.

2.2.4 Discussion on chemical, and pharmaceutical aspects

Relevant ICH/CHMP guidelines and Pharmacopoeial requirements have been followed in the quality documentation.

Information on development, excipients, manufacturing process, analytical methods, packaging 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. At the time of the CHMP opinion, there were no unresolved quality issues which could have an impact on the benefit/risk ratio of the medicinal product.

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.

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.

2.3.2 Pharmacology

In vitro, AT1 receptor antagonists inhibit the contractile effects of AII in all vascular smooth muscle preparations. In vivo, they prevent and reverse all the known effects of AII including: rapid pressure response; slow pressure response; stimulatory effects on the peripheral sympathetic nervous system; CNS effects such as thirst, vasopressin release and sympathetic tone; release of adrenal catecholamines; secretion of aldosterone; direct and indirect effects of AII on the kidneys; growth-promoting actions. Furthermore, they reduce arterial blood pressure in animals with renovascular and genetic hypertension, and in transgenic animals over-expressing the renin gene, but have little effect in animals with low-renin hypertension. They are highly selective in that they do not displace ligands

that bind to calcium channels or adrenergic, muscarinic, dopaminergic, opioid or neurotensin receptors, and do not antagonise the actions of vasopressin, catecholamines, acetylcholine, serotonin, bradykinin or histamine.

Mechanistically, AII is formed from AI in a reaction catalysed by ACE. AII, being the principal pressor agent of the RAAS, elicits effects that promote hypertension, including vasoconstriction, stimulation of the synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. AII antagonists such as telmisartan prevent the vasoconstrictor and aldosterone-secreting effects of AII by selectively blocking the binding of AII to the AT1 receptor in the cell membranes of various tissues including vascular smooth muscle and the adrenal gland. This action is therefore dependant upon the pathways of AII synthesis.

AT2 receptors are also present in a wide variety of tissues but they are not known to be associated with cardiovascular homeostasis. In any event, the selectivity of telmisartan comes from its >3000 times greater affinity for AT1 receptors compared with AT2's,

ACEI also block the renin-angiotensin system by inhibiting the biosynthesis of AII from AI, and are widely used in the treatment of hypertension and CHF. ACEI also inhibit the degradation of bradykinin (which is also catalysed by ACE), a property not associated with telmisartan. It is possible that the lack of activity in this respect may make telmisartan less likely to be associated with the side effect of cough that is experienced by some patients taking ACEI.

Blockade of the AT1 receptor inhibits the negative regulatory feedback of AII on renin secretion, but the resulting elevated plasma-renin activity (PRA) and circulating levels of AII do not overcome the effect of telmisartan on blood pressure. It is also pertinent that telmisartan does not bind to, or affect, other receptors or ion channels important in cardiovascular regulation.

In vivo, telmisartan has shown hypotensive activity in the main species used in the toxicology (rat and dog) and in rabbits, cynomolgus monkeys and marmosets. Telmisartan reduced diastolic blood pressure in normotensive rats, dogs and rabbits. In AII-induced hypertension in rats, telmisartan dose-dependently lowered blood pressure after oral, i.v. or i.d. administration, identifying it as a non-competitive receptor antagonist. It also lowered blood pressure in renin-dependent hypertensive rats (in which losartan was 3 times less potent) and in renal hypertensive rats. The effect was long-lasting, particularly in the dog, which appeared to be the more sensitive species. The enduring effect could result from slow dissociation or from slow off-rate of telmisartan from its binding sites. In sodium-depleted normotensive cynomolgus monkeys, telmisartan elicited up to a 42% reduction in MAP without affecting heart rate. Increases in PRA and plasma AII levels suggested that increased PRA maybe a consequence of blocking AII receptors in renin-sensitive tissues. Furthermore, telmisartan inhibited the AII pressor response in anaesthetised marmosets.

Telmisartan also has a cardioprotective function that has been demonstrated in rats. As well as lowering blood pressure in the streptozotocin-induced diabetic rat, it also lowered cholesterol, very low density lipoproteins and triglycerides, and prevented cardiac hypertrophy. In another model, telmisartan improved cardiovascular remodelling associated by the production of e-NOS through PPAR-γ, inhibition of the Rho-kinase pathway and suppression of oxidative stress.

In a series of studies unrelated to its therapeutic activity, telmisartan at very high doses in rats and guinea pigs had some non-specific inotropic activity giving rise to ECG changes, ventricular tachycardia and AV-block with bradycardia; importantly, there were no ECG changes in the comprehensive programme of toxicity studies. In renal function tests in rats, telmisartan had diuretic and natriuretic effects and elevated BUN and creatinine levels; these changes were prevented in animals that were sodium-loaded. It was also reported that telmisartan protects against the nephrotoxic effects of cyclosporin A in minipigs and of diatrizoate in rats. Telmisartan attenuated glitazone-induced increases

in body fat mass in genetically obese rats and rats fed a high-fat diet. It did not affect bradykinin-induced bronchoconstriction in anaesthetised guinea pigs. Finally, in CNS studies, telmisartan had no muscle-relaxant activity in mice, and did not affect spontaneous motor activity or hexobarbital sleeping time in rats.

There is no nonclinical information on drug interactions with telmisartan, but clinical data exist in relation to co-administration with digoxin, diuretics, NSAID's, highly protein-bound drugs and drugs that are metabolised by CYP2C19.

2.3.3 Pharmacokinetics

The pharmacokinetics of telmisartan was investigated by the oral and i.v. routes in rats, mice, dogs and rabbits (the main species used in the toxicology). In addition, toxicity studies had complementary toxicokinetics.

Orally administered telmisartan was rapidly absorbed in rats, mice and dogs, but more slowly in rabbits. Absorption was high in rats and mice, with absolute bioavailability of 56-75%. It was lower in dogs though less so when administered after food. In mice and humans, Cmax and AUC were higher in F, but there were no clear gender differences in rats or dogs.

Cmax after an oral dose of 1 mg/kg was similar in rats, dogs and humans, but higher in mice and rabbits. The t½ was reasonably similar in rats, mice and dogs, but was longer in rabbits and humans. In rats, mice and dogs, the compound-related material in plasma was predominantly parent drug whereas, in rabbits, there were roughly equal amounts of parent and metabolite(s). Dose-proportionality with single rising doses was apparent at lower doses in rats and dogs but, at higher doses, it was greater than proportional; similar non-proportionality occurs in humans. In rabbits, plasma concentrations 24 hours after dosing were high, indicating constantly high exposure during repeated daily dosing.

Orally administered telmisartan concentrates predominantly in the plasma fraction of the blood in all species, and correlates with the very high binding to plasma proteins (around 99%). The high degree of binding results in relatively slow metabolism of the parent compound.

Telmisartan is rapidly distributed into a volume of distribution greater than total body water (5.3L/kg in rats, and 1.7-3.0 L/kg in dogs). Tissue distribution studies in rats showed the highest concentration to be in the liver, with lower levels in blood, lung, renal cortex and myocardium; only very low levels were identified in the CNS. In pregnant rats, telmisartan crossed the placenta and was identified in foetal liver, kidney and lung where, 24 hours after dosing the dam, levels were higher than in maternal blood at that time.

After absorption from the oral route, telmisartan appears predominantly as parent compound (80-90%) in the plasma. It was readily glucuronidated in all microsomal fractions except lung, and its affinity for liver enzymes was greater than those from kidney or small intestine. The rate of metabolism in the liver was slow and drug was retained in the liver, but the rate of elimination of the glucuronide was rapid. The main metabolite in rat and human systems was telmisartan 1-O-acylglucuronide. The metabolism of telmisartan is similar in rats, mice and dogs though, in mice, a glycoside of telmisartan was also identified and accounted for 5-11% of the administered dose.

In all species including humans, telmisartan is preferentially eliminated via the bile into the faeces, with <1% excreted in the urine. There was virtually no enterohepatic recycling of parent drug and only about 10% of the acylglucuronide. In lactating rats, the levels of telmisartan-related material secreted in the milk were about twice those in plasma.

2.3.4 Toxicology

Single dose toxicity

The single-dose studies provided limited useful information. An oral dose of 2000 mg/kg had no effects in rats, while dogs given 100 mg/kg had white material (presumably drug) in their faeces. Rats dosed i.v. at 200 mg/kg showed depressant effects and, amongst other post-mortem changes, discoloured kidneys and gastric haemorrhage.

Repeat dose toxicity

A full regulatory programme of toxicity studies up to 12 months' duration was conducted in rats and dogs. In all repeated dosing studies, there was a commonality of effects in the kidney and gastrointestinal tract, irrespective of whether the drug was administered by gavage, in the diet or intravenously (i.v. studies are not considered in this document). The primary target organs in rats, dogs and mice were kidneys and gastrointestinal tract.

The kidney changes were associated with elevated circulating levels of BUN and creatinine and alterations in electrolyte concentrations. In rats and dogs, there was juxtaglomerular hypertrophy and hyperplasia of the afferent glomerular arterioles; the effects were blocked by sodium loading in rats. They probably arose as a consequence of exaggerated pharmacology; blockade of AII induced inhibition of renin release, thereby stimulating renin-producing cells. Similar changes occur with other sartans and with ACEI, and are considered not relevant to therapeutic doses in patients. Telmisartan was also associated with renal tubular changes in normotensive dogs, which were consistent with hypotension reducing renal perfusion, leading to tubular hypoxia and consequent tubular cellular degeneration and necrosis. In hypertensive patients, the objective of telmisartan treatment would be to restore normal blood pressure; under these circumstances, the hypotensive states necessary for reductions in renal blood pressure and consequent pathology would not arise.

Gastrointestinal erosion and ulceration, and mucosal and submucosal inflammation and subsequent fibrosis, occurred predominantly in rats and rabbits; dogs were less sensitive and mice were not affected. The effects were not a consequence of local irritation because i.v. administration (in studies not reviewed here) gave rise to similar lesions. The precise mechanism is unknown but, like the renal changes, the gut changes can be ameliorated in rats by salt-loading.

There were also consistent anaemic changes (such effects are known to occur with ACEI and AII antagonists as a result of reductions in erythropoietin, presumably due to the decreased influence of AII on the kidney). The effects were generally time- and dose-related in both incidence and severity, and are considered to be a consequence of exaggerated pharmacodynamic activity. They can be prevented by salt-loading in rats.

The decrease in heart weight recorded in most toxicity studies probably reflected a reduction of hypertrophied cardiomyocytes to their normal size, rather than any reduction from the normal. The reduction has been attributed to the absence of trophic effects of AII on growing cardiomyocytes and the prevention of cardiac hypertrophy. There is no loss of contractile function in the smooth muscle cells, so cardiac function is not affected. This is also a class effect with AII antagonists and ACEI.

Genotoxicity

The recommended range of genotoxicity studies followed accepted protocols and gave uniformly negative results.

Carcinogenicity

Carcinogenicity studies in rats and mice used high multiples of the maximum human exposure level as justification for setting the highest dose level; furthermore, in rats, it is possible that the MTD was attained. There was no effect on survival, and the toxicological findings were consistent with those in the repeated-dose studies. In both species, statistical analyses of the results revealed no significant positive trend or increase in incidence of neoplasms in any of the telmisartan-treated groups compared with controls. This conclusion was supported by the absence of genotoxicity in a full battery of mutagenicity studies.

Reproduction Toxicity

Reprotoxicity studies with telmisartan in rats and rabbits followed the conventional Segment I, II and II approach. Complementary toxicokinetics revealed little difference in exposure from non-pregnant rats; there was constant systemic exposure at all doses and dosing periods in both rats and rabbits; furthermore, in rats, drug crosses the placenta and is secreted in the milk of lactating animals. In both species, toxicity was apparent primarily as reductions in food consumption and bodyweight gain. There was no effect on fertility in rats and no evidence of teratogenicity in either species. In weanling rats, a short delay in eye-opening was probably a consequence of reduced bodyweight gain. In rabbits, there was an all-or-nothing effect on intrauterine loss; in some dams, there was total resorption while, in similarly treated animals, foetal development was not affected.

2.3.5 Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Telmisartan Teva Pharma manufactured by Teva Pharma B.V. is considered unlikely to result in any significant increase in the combined sales volumes for all telmisartan containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.6 Conclusion on the non-clinical aspects

The non-clinical overview presented by the applicant provided an adequate overview of the pharmacological, pharmacokinetic and toxicological aspects of telmisartan. There were no major issues raised during the assessment from a non-clinical point of view.

2.4 Clinical Aspects

2.4.1 Introduction

This is an application for oral tablets containing telmisartan. To support the marketing authorisation application the applicant conducted a bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for the assessment.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

Exemption

Dissolution profiles of telmisartan

The test and reference dissolution profiles were compared using a validated discriminatory dissolution method.

Justification for biowaiver

The results of the bioequivalence study conducted with the 80 mg tablets could be acceptable for the 20 mg and 40 mg strength because the following criteria for a biowaiver have been fulfilled:

1. The pharmaceutical products are manufactured at the same site by the same manufacturer and manufacturing process.

2. The qualitative composition of the different strengths is the same.

3. The composition of the strengths is quantitatively proportional.

The pharmacokinetics of orally administered telmisartan are nonlinear over the dose range 20–160 mg, with greater than proportional increases of plasma concentrations (Cmax and Telmisartan 20 mg, 40 mg and 80 mg Tablets AUC) with increasing doses. The selection of the 80mg dose to establish bioequivalence is in line with the Questions and Answers on the Bioavailability and Bioequivalence guideline EMEA/CHMP/EWP/40326/2006, which indicates that a single strength study may be acceptable provided that the study is conducted on the highest dose for drugs with a demonstrated greater than proportional increase in AUC or Cmax with increasing dose, as is the case with telmisartan. The biowaiver was granted for the lower strengths.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study. No new pharmacodynamic studies and no new therapeutic equivalence studies were submitted.

2.4.2 Pharmacokinetics

Methods

Study design

This is an open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover study. Subjects were randomly assigned to one of the two dosing sequences AB or BA under fasting conditions. Each subject received either an 80mg telmisartan generic tablet (Test) or a Micardis 80mg tablet (Reference), with 240ml water, after an overnight fast, according to a computer generated randomisation list. Following a 14-day washout period, the subjects received the alternative formulation under identical conditions. During each study period, blood samples were taken pre-dose and at 0.125, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00, 12.0, 24.0, 48.0 (± 0.5), 72.0 (± 0.5), 96.0 (± 0.5) and 120 (± 0.5) hours after drug administration. Plasma was harvested from these samples and assayed for telmisartan using a validated LC/MS/MS method.

The design employed was considered by the CHMP appropriate for bioequivalence studies. The selection of the 80mg dose to establish bioequivalence is in line with the bioequivalence guideline EMEA/CHMP/EWP/40326/2006, which indicates that a single strength study may be conducted on the highest dose for drugs with a demonstrated greater than proportional increase in AUC or Cmax with increasing dose.

The study was complying with GCP, as claimed by the applicant.

Test and reference products

Treatment		
	Test (A)	**Reference (B)**
Name:	telmisartan	telmisartan (Micardis)
Unit dose:	80 mg	80 mg
Regimen:	single dose of 1 x 80 mg tablet per subject in accordance with the randomisation scheme	single dose of 1 x 80 mg tablet per subject in accordance with the randomisation scheme
Lot/Batch No.:	K-36856 (Batch No.)	706944
Expiry date:	Not available	07 2011
Manufacturing date:	May 23, 2006	Not available
Company Responsible for Manufacturing:		Boehringer Ingelheim International GmbH, Germany

The size of the biobatch was considered acceptable. The Product Certificates of the Test and Reference products were missing but were provided by the applicant during the evaluation of the application. It was concluded that tablets used in bioequivalence study have the same pharmaceutical characteristics as the tablets to be marketed.

Population(s) studied

Sixty healthy adult subjects (43 males and 17 females of non-childbearing potential) aged between 20 and 55 years (mean 39 ± 10), with a body mass index (BMI) of between 20.3 and 29.9 (mean 26.1 ± 2.4) and a weight range of 48.7 to 96.9kg (mean 74.3 ± 9.7) participated in the study. A total of 58 subjects completed the study and were included in the pharmacokinetic analysis. The following subjects did not complete the study:

Subject No. 28 withdrew prior to period 2 of the study due to seborrheic dermatitis of the nose.

Subject No. 52 failed to attend for period 2 of the study.

Analytical methods

Telmisartan concentration in plasma samples was determined by a HPLC/MS/MS method. The method was validated according Bioanalytical Validation Guideline of the FDA.

Pharmacokinetic Variables

The pharmacokinetic parameters of interest in this study were: AUC0-t, AUC0-inf, AUCt/inf, Cmax, Residual area, Tmax, Kel and T½ el.

Statistical methods

Analysis of Variance (ANOVA) was performed on log-transformed AUC0-t, AUC0-inf and Cmax data. ANOVA was also performed on the untransformed Kel and T½ el data. Wilcoxon's Signed-Rank test was carried out to compare Tmax between treatments. The ratios of least-squares means and 90% geometric confidence intervals were calculated for log-transformed AUC0-t, AUC0-inf and Cmax.

Covariates in the ANOVA model: were: group, sequence, sequence*group, subject (sequence*group), period (group), treatment and treatment*group. Standard statistical model and industry standard statistical software (SAS) were used.

Results

Pharmacokinetic Parameters

Parameters		Test (Telmisartan (A)) Mean	SD	CV (%)	Reference (Micardis® (B)) Mean	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	1917.82	1397.89	72.89	1921.13	1322.21	68.82
AUC_{0-inf}*	(ng·h/mL)	2085.11	1498.08	71.85	2086.25	1452.07	69.60
$AUC_{t/inf}$*	(%)	93.35	7.45	7.99	93.06	7.55	8.12
C_{max}	(ng/mL)	323.06	408.53	126.46	297.47	282.36	94.92
Residual area*	(%)	6.65	7.45	112.09	6.94	7.55	108.91
T_{max}	(h)	1.36	1.05	76.74	1.26	1.13	89.91
T_{max}**	(h)	1.00	0.50	-	0.750	0.500	-
K_{el}*	(h^{-1})	0.0284	0.0121	42.39	0.0293	0.0125	42.49
$T_{½ el}$*	(h)	29.83	19.17	64.27	30.46	21.58	70.85

*For these parameters, N = 57.

**Medians and interquartile ranges are presented.

Telmisartan (A) vs Micardis® (B)

	AUC_{0-t}	AUC_{0-inf}*	C_{max}
Ratio[1]	97.73%	98.44%	101.43%
90 % Geometric C.I.[2]	92.92% to 102.78%	93.04% to 104.14%	90.85% to 113.23%
Intra-Subject CV	16.07 %	17.89 %	35.96 %

[1] Calculated using least-squares means according to the formula: $e^{(\text{Telmisartan (A) - Micardis® (B)})} \times 100$

[2] 90% Geometric Confidence Interval using ln-transformed data

*For this parameter, N = 57

Conclusions

The presented bioequivalence study confirmed that the test product (telmisartan 80mg tablets) is bioequivalent to the Reference formulation (Micardis 80mg tablets, manufactured by Boehringer Ingelheim International GmbH, Germany) with respect to rate and extent of availability.

The analytical validation reports are compliant with regulatory requirements.

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

The residual area was 6.65% for the test product and 6.94% for the reference product, indicating that the pharmacokinetic time points were adequate to detect 80% of the AUC to infinity, for both products.

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.

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 Conclusions on clinical aspects

The efficacy and safety profile of telmisartan in the indication claimed for Telmisartan Teva Pharma (i.e. treatment of essential hypertension) is well known and no additional clinical studies are needed.

A bioequivalence study was conducted and confirmed that the test product (telmisartan 80mg tablets) is bioequivalent to the Reference formulation (Micardis® 80mg tablets, manufactured by Boehringer Ingelheim International GmbH, Germany) with respect to rate and extent of availability.

The recommended dosage and method of administration of the generic product Telmisartan Teva Pharma 20 mg, 40 mg and 80 mg tablets is the same as that recommended for the reference product Micardis 20 mg, 40 mg and 80 mg tablets.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

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

Risk Management Plan

The CHMP did not require the applicant to submit a risk management plan because the application concerns a generic for a reference medicinal product for which no safety concern requiring additional risk minimisation activities has been identified.

PSUR cycle

The PSUR cycle for the product will follow PSURs submission schedule for the reference medicinal product Micardis, which is on a yearly cycle, having 11 April 2012 as its data lock point.

2.6 User consultation

The results of the user consultation with target patients 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 application concerns a generic version of telmisartan tablets. The reference product Micardis is indicated for essential hypertension in adults and for cardiovascular prevention, for the reduction of

cardiovascular morbidity in patients with manifest atherothrombotic cardiovascular disease (history of coronary heart disease, stroke or peripheral arterial disease) or type 2 diabetes mellitus with documented target organ damage. No nonclinical studies have been provided for this generic 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 forms the pivotal basis with a open-label, single-dose, randomised, two-period, two-sequence, two-treatment, crossover design. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. A single dose under fasting conditions study is considered appropriate in view of the fact that telmisartan does not accumulate during repeated administration. 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 Telmisartan 80 mg tablets met the protocol-defined criteria for bioequivalence when compared with the European brand product Micardis 80 mg tablets (manufactured by Boehringer Ingelheim International GmbH, Germany). The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

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

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 Telmisartan Teva Pharma in the treatment of essential hypertension in adults is favourable and therefore recommends the granting of the marketing authorisation.

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Pharmacovigilance System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.