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Committee for Medicinal Products for Human Use (CHMP)

# Assessment Report

# Telmisartan Actavis

**International Non-proprietary Name**: Telmisartan

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 Actavis Group PTC ehf. submitted on 1 May 2009 an application for Marketing Authorisation to the European Medicines Agency for Telmisartan Actavis, 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 Article 10(1) of Directive 2001/83/EC, as amended.

The application concerns a generic medicinal product as defined in Article 10(1) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Community on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC, as amended.

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 and 80 mg tablets**
- Marketing authorisation holder: **Boehringer Ingelheim International GmbH**
- Date of authorisation: **16/12/1998**
- Marketing authorisation granted by: **Community**
- Marketing authorisation numbers: **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**
- Marketing authorisation number: **EU/1/98/090/008**
- Bioavailability study number: **Study 1040**

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

| | |
|---|---|
| **Rapporteur** | **Pierre Demolis** |

**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 application was received by the Agency on 1 May 2009.
- The procedure started on 24 June 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 September 2009.
- During the meeting on 19-22 October 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 22 October 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 11 March 2010.
- The Rapporteur circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 April 2010.
- During the CHMP meeting on 17-20 May 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 26 May 2010.
- The Rapporteur circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding issues to all CHMP members on 3 June 2010.
- During the meeting on 21-24 June 2010, 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 Actavis on 24 June 2010. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 24 June 2010.

# 2. Scientific discussion

## *2.1. Introduction*

Telmisartan Actavis tablets is a generic medicinal product containing the active substance telmisartan. The reference medicinal product is Micardis tablets authorised 16 December 1998.

Telmisartan 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. 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 bradykin in mediated 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.

The reference product was authorized in the Community on 16 December 1998 for Boehringer Ingelheim International GmbH. Bioequivalence to the reference product was demonstrated at the highest strength. Regarding the lower strengths of Telmisartan Actavis 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 Telmisartan Actavis is identical to the indication of the reference medicinal product.

The therapeutic indication of Telmisartan Actavis 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

Telmisartan Actavis 20mg, 40mg and 80mg are presented as immediate release white uncoated tablets which differ from each other in mass, shape (20mg: round flat, 40mg: oval biconvex, 80mg: oval biconvex), by the presence of a break line for the 40mg strength, and by a different logo for the 80mg strength (20mg: logo T on one side, 40mg: logo T on one side, 80mg: logo T1 on one side).

They contain 20mg, 40mg and 80mg of telmisartan as drug substance, respectively. All the strengths are dose proportional and therefore are produced from the same powder mixture.

The formulation comprises the following excipients: Potassium hydroxide pellets, Mannitol eur DC, Povidone, Croscarmellose sodium and Magnesium stearate.

The tablets are packaged in Alu/Alu blisters or in HDPE bottles/LDPE lids with desiccant.

## 2.2.2. Active Substance

The active substance is telmisartan, a benzimidazole derivative antagonist of subtype 1 angiotensin II receptors (AT1) intended for the treatment of essential arterial hypertension.

Telmisartan is a well known active substance described in Ph. Eur.. Telmisartan is chemically described as 4'-[(1,4'-dimethyl-2'-propyl [2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-[1,1'-biphenyl]-2-carboxylic acid (see figure 1).

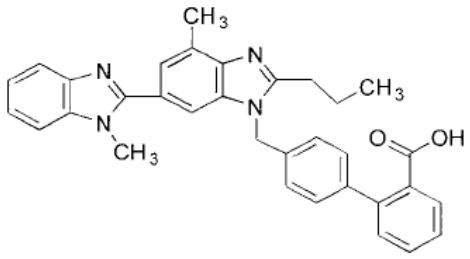


Figure 1: Chemical structure of telmisartan

It is a white to off-white crystalline powder, practically insoluble in water, but freely soluble in organic solvents. Telmisartan has no chiral centres and exhibits no stereoisomerism. 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 the same polymorphic form, i.e., polymorph form A.

**Manufacture**

Telmisartan is manufactured by two different manufacturers. The Active Substance Master File (ASMF) procedure was followed for the active substance for both manufacturers. Letters of access have been received from each manufacturer.

Telmisartan is synthesised in either 2 or 3 steps depending on the ASMF Holder. There are either one or two steps involving chemical reactions and for both manufacturers the last step involves purification of the active substance. Full description of the manufacturing was provided in the restricted part of the ASMF.

**Specification**

Telmisartan is routinely controlled according to the Ph.Eur. monograph and additional specification. A common set of specification includes the following tests: appearance, solubility, identification (IR), related substances (HPLC), loss on drying, sulfated ash, assay (HPLC), heavy metals, residual solvents (GC), water content (Karl-Fischer), particle size (X-ray diffraction) .

The proposed specifications are based on the European Pharmacopoeia. Specifications for residual solvent are in compliance with ICH guideline Q3C. Impurities have been evaluated and found to be acceptable from the point of view of safety.

The non compendial methods used, e.g. for residual solvents have been satisfactory validated. In-house methods have been sufficiently described and correctly validated.

Batch analysis from both manufacturers has been included in the application. All batches comply with the specifications set and confirm the consistency and uniformity of the process.

For both manufacturers, the active substance is stored in polyethylene bags. The bags are placed into either a HDPE or fibre drum. Specifications and test methods used for packaging control are described and a certificate of analysis is enclosed. The food grade certificate is provided.

**Stability**

Stability studies have been performed on three batches of active substance of each manufacturer under ICH long-term conditions (25°C/60% RH) and accelerated conditions (40°C/75% RH).

Parameters tested during stability studies included appearance, identification, water content, assay and related substances. The analytical methods are the same as those used for the control of the active substance.

Forced degradation studies with telmisartan under various conditions (heat, acidic, alkaline conditions, under oxidizing conditions) and photo stability were investigated. The analytical method used in the stability studies are the same as the method used for related substances described in section 3.2.S.4. The results show that telmisartan is mainly affected by basic and oxidising conditions. The active substance is also sensitive to acidic and light conditions since a slight degradation was perceived in these conditions. The active substance showed to be unaffected by temperature. Results also showed that the HPLC method used in this study is stability indicating.

Stability data under long-term and accelerated conditions, as well as forced degradation studies support the re-test period.

## 2.2.3. Medicinal Product

**Pharmaceutical Development**

The objective was to develop an immediate-release, conventional tablet with a relatively rapid drug release similar to that of the reference product. The objective was to produce dose proportional tablets of similar size to the reference product Micardis.

Since the active substance is dissolved during manufacture, the particle size of Telmisartan was not a critical parameter for the production of Telmisartan tablets. Nevertheless, micronised material was deemed necessary to improve its solubility. Polymorphic conversion of Telmisartan (from Form A to amorphous form) during manufacturing process was documented. Data provided showed that the conversion was reproducible. Physical stability of the amorphous state upon storage has been demonstrated through compliant dissolution profiles during stability studies.

The manufacturing process selected was fluid bed granulation in order to improve the flow properties of the raw materials and to increase the solubility of the active substance. This manufacturing process also ensured similar dissolution profiles to the reference product.

Excipients used in the formulation were all compendial, well known and widely used for this dosage form. The excipients used include: mannitol (filler), povidone (binder), croscarmellose sodium (disintegrant), potassium hydroxide (alkalising agent), magnesium stearate (lubricant), purified water (granulation liquid), and ethanol 96% (granulation liquid). The excipients selected were justified with regard to the manufacturing process. All excipients used for the manufacture of the drug product are inert and no incompatibility between them and the drug substance is expected from the stability tests performed.

Telmisartan tablets do not contain any excipient originating from human or animal. Therefore no TSE risk is anticipated.

### *In-vitro* dissolution

Dissolution comparison was made between the test product and the reference product at three pH media: pH 1.1 (HCl 0.1 M), pH 4.5 (SIF) and pH 7.5 (Phosphate buffer).

The dissolution profiles of the bioequivalence test and reference products are similar in 0.1M HCl ($f_2$ = 65.0). Differences between test product and reference product used in the bioequivalence study at pH 7.5 were observed. However, the differences in the formulation of the two products could have contributed to the slower dissolution profile of the Telmisartan 80mg in pH 7.5 buffer. The differences found in the pH for the two products, due to the basic Meglumine used in the Micardis tablets could have contributed to different profiles. In addition, the longer disintegration time observed for the Micardis compared to Telmisartan tablets could have also been a consequence of the different particle size of the active substance used and/or to differences in the manufacturing process.

Results of comparative dissolution testing between the three strengths of the generic product in HCl 0.1 M in the buffers pH 4.5 and pH 7.5 have been provided. Similar *in vitro* dissolution was demonstrated at all conditions within the applied product series, i.e. between additional strengths and the strength used for bioequivalence testing (f2 > 50 in medium pH 1.1; without necessity of mathematical evaluation in media pH 4.5 and 7.5). No difference was seen between the three proportional strengths of the generic product and therefore, comparison with the respective reference product for the 20mg and the 40mg strengths was found to be unnecessary. Although *in vitro* dissolution of the generic product is faster than the reference product over the first 45 minutes, this is deemed acceptable since BE of the generic product and the reference product has been demonstrated by appropriate bioequivalence studies.

Various packaging materials were tested during stability studies on development batches. The results showed that the most suitable packaging for telmisatan is Aluminium/ Aluminium and HDPE containers with desiccant.

### *In-vivo* bioavailability

Telmisartan Actavis 80mg (Pilot batch No. D31432) was used in the bioequivalence study (Study No. 1040) *versus* reference product Micardis 80mg (Batch No. 606034) from the German market. Since Micardis has been authorised through the Centralised Procedure the composition in all EU countries is exactly the same (EU/1/98/090). A comparison of the physicochemical characteristics and the impurity profile was provided between test and reference batches. No significant difference could be found. A biowaver for telmisartan Actavis 20 mg and 40 mg strengths tablets was granted since the formulation is proportional and the strengths not tested in the bioequivalence study show similar behaviour in the whole range of physiological pH values in the *in vitro* dissolution tests.

### Manufacture of the Product

The manufacturing process for Telmisartan Actavis is as follows: dissolution, fluid-bed granulation, drying, blending and tabletting. An adequate flow-chart was provided and the different steps of the manufacturing process were described together with the equipment and operating parameters (e.g. sieve sizes, mixing times). The Applicant gave a Letter of Undertaking and committed to update the operating parameters and capacity of the equipment as a function of batch size based on the validation data obtained from production-scale batches.

The manufacturing process has been satisfactorily validated at pilot-scale at the proposed manufacturing sites. Process validation has been performed on the first pilot-scale batch. The following parameters have been validated: core granulate, final blend and compression and finished product. The manufacturing process was challenged by tabletting the three tablet strengths at minimum and maximum hardness levels and at three compression speed levels, without any significant effect on average mass, mass distribution, disintegration time, or breakability for the 40mg strength. Maximum hardness tablets of the three strengths were tested for dissolution. They all comply with the retained criteria for dissolution.

The validation results demonstrate batch-to-batch consistency. The analytical results are consistent and comply with the proposed drug product specification.

**Product Specification**

Adequate release and shelf-life specification have been presented for the finished product and include: visual description, identification (HPLC and UV), uniformity of dosage unit (PhEur), loss on drying, average weight, resistance to crushing (PhEur), friability (PhEur), disintegration (PhEur), assay (HPLC), related substances (HPLC), dissolution (PhEur), microbiological quality (PhEur), and breakability test (PhEur). Analytical methods have been well described and validated.

The proposed limits for the impurities are in accordance with the ICHQ3B guideline.

Batch analysis results for 10 pilot batches representative of all strengths (20 mg, 40 mg and 80 mg) of Telmisartan Actavis manufactured at both sites, using active substance sourced from the two proposed manufacturers of the active substance confirm consistency and uniformity of manufacture and indicate that the process is reproducible.

**Stability of the Product**

Stability studies under ICH long-term, intermediate and accelerated conditions (i.e. 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH) have been carried out on 10 pilot batches representative of all strengths (20 mg, 40 mg and 80 mg) and manufactured at both sites, using active substance sourced from the two proposed manufacturers of the active substance. The results showed that at 30°C/ 65 % RH the impurities content remained within specification with no evidence of loss of potency. No significant changes were observed for any other parameter tested. After 6 months storage at 40°C/75 % RH similar results were obtained. The long-term conditions (25°C/60% RH) were only tested if significant change is observed at 30°C. An in-use stability study was also conducted in open HDPE containers for up to 6 months at 25°C/60% RH.

All the parameters from the finished product specification were tested during the stability studies. No significant changes for the parameters tested could be observed during the stability studies. The results support the shelf life.

## 2.2.4. Discussion on chemical, and pharmaceutical aspects

Telmisartan is routinely controlled according to Ph. Eur. monograph. In-house methods have been sufficiently described and correctly validated. Stability studies according to the relevant EU/ICH stability guidelines have been submitted.

The pharmaceutical development of the formulation and the manufacturing process were satisfactorily documented. A bioequivalence study was performed on the test product Telmisartan Actavis 80mg tablet *versus* the reference product Micardis 80mg tablet sourced from the German market. Additionally, comparative *in vitro* dissolution profiles of the lower strengths, including the biobatch test product, and the biobatch reference product were provided to support the essential similar character.

The manufacturing process was described and the critical steps identified. The manufacturing flow-chart was provided with suitable in-process controls. The manufacturing process is adequately validated at pilot scale at the proposed manufacturing sites.

The routine specifications and tests methods proposed for the drug product will adequately control the quality of the product. Analytical methods were well described and validated in agreement with ICH guidelines.

Batch analyses were presented and the results showed that the drug product meets the specifications proposed.

Both container-closure systems consisting of either Aluminium/Aluminium blisters or HDPE bottles with LDPE lids with desiccant were found to be suitable to ensure the quality of the finished product as shown by the stability data.

The conditions used in the stability studies comply with the ICH stability guideline. The control tests and specifications for drug product were adequately established.

### 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product have 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. Observed differences are minor and are not considered to be clinically relevant.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe.

## *2.3. Non-Clinical aspects*

Since this application is a generic application referring to the originator product (Micardis), no new non-clinical studies on the pharmacology, pharmacokinetics and toxicology of Telmisartan have been submitted. Telmisartan is a widely used well-known active substance. Its pharmacodynamic, pharmacokinetic and toxicological properties are well characterised. No further studies are required and the applicant has justified why no such data was provided.

The non-clinical overview submitted by the applicant provides a sufficient outline of the available literature concerning the non-clinical pharmacology, pharmacokinetics and toxicology of Telmisartan.

No Environmental Risk Assessment was submitted. This product is intended to substitute other identical products on the market. Therefore, the approval of this product does not result in an increase of the total quantity of telmisartan released into the environment. It does not contain any component which results in additional hazard to the environment during storage, distribution, use and disposal. 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.

### *GCP*

The applicant has provided a statement to the effect that the bioequivalence study was performed in accordance with GCP and the ethical requirements of Directive 2001/20/EC.

## 2.4.2. Pharmacokinetics

Pivotal Study 1040

- Methods

The study was designed according to an open-label, randomised, single-dose, 2-way crossover, 2-sequence classical scheme with a washout period of 14 days between dosing. Subjects were randomly assigned to one of the two dosing sequences.

The objective of this study was to compare the relative bioavailability of Telmisartan 80 mg Tablets and Micardis 80 mg Tablets in normal, healthy male and female volunteers under fasting conditions.

Sixty-six (66) subjects were planned to be analyzed. Fifty-eight (58) subjects completed the study. Six (6) subjects withdrew due to personal reasons and two (2) subjects withdrew due to AEs.

Fifty-eight (58) subjects were included in the statistical analysis.

- Results

Telmisartan: Pharmacokinetic parameters (AUC and Cmax: arithmetic mean ± SD, tmax: median, range): Single 80 mg oral dose (n=58).

| **Treatment** | **$AUC_{0-t}$** npg*h/ml | **$AUC_{0-\infty}$** ng*h/ml | **$C_{max}$** ng/ml | **$t_{max}$** h |
|---|---|---|---|---|
| **Test** | 1537.90 | 1865.50 | 266.13 | 1.00 |
| **(S.D.)** | (2034.16) | (2581.17) | (327.49) | [0.50-5.00] |
| **Reference** | 1535.62 | 1920.03 | 311.86 | 0.84 |
| **(S.D.)** | (2057.61) | (2462.45) | (416.17) | (0.33-4.00) |
| ***Ratio (90% CI)** | [94;107]% | [91; 104]% | [76;95]% | |
| **Point estimate** | 100 % | 97 % | 85 % | |
| **Intra-subject CV (%)** | 18.87 % | 16.62 % | 36.21 % | |
| **$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity<br>**$AUC_{0-t}$** area under the plasma concentration-time curve from time zero to t hours<br>**$C_{max}$** maximum plasma concentration<br>**$T_{max}$** time for maximum concentration : mediane, min and max | | | | |

**log-transformed values*

- Discussion

This submission is a generic application; therefore, new clinical studies are neither required nor submitted.

The application contains an adequate review of published literature concerning aspects of pharmacology, pharmacodynamic, efficacy and safety of Telmisartan and in addition one bioequivalence study (study 1040) was provided.

The PK profile of Telmisartan is not linear over the therapeutic dose range (20-160 mg). The bioavailability increased more than proportionally to the dose and the terminal elimination half-life is about 24 hours.

The conventional CI for Log transformed AUCt, AUCinf are within the [80;125]% acceptance range.

A statistically significant difference between the Test and Reference is observed with Cmax. The point estimate for the ratio is 0,85 and the 90% CI is not included in the standard [80;125] acceptance range. No significant difference in Tmax was evidenced by the non parametric test.

The pilot study 1022 (semi-replicate crossover design) provided by the applicant was adequately designed to allow a reliable estimation of the intra-subjects variability. For instance, the CV (%) related to Cmax intra-subject variability of the reference drug product is approximately 45%. Therefore, telmisartan could be considered a highly variable drug (HVD) and the acceptance range for Cmax ratio CI could potentially be widened accordingly. As stated by the revised NfG on the investigation of BE, the acceptance range estimated using the scaled-average-BE approach would be [72.15; 138.59]%. The CI for Cmax estimated in the pivotal study (Study 1040) was [76;95]%.

In order to draw definite conclusions on the BE of the Test and reference drug products, the applicant was requested by CHMP to perform a re-analysis of the pivotal study data (study 1040) including subjects 59 and 61. From the results with the subjects included, the 90% confidence interval of the test/reference (T/R) ratio of the least square means for AUCt parameter is contained within 0.80 and 1.25 range, and the 90% confidence interval of the test/reference (T/R) ratio of the least square means for the Cmax parameter is contained within the extended acceptance range ([75; 133] %).

In the NfG on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), bioequivalence is defined as: ”Two medicinal products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if their bioavailabilities after administration in the same molar dose are similar to such degree that their effects, with respect to both efficacy and safety, will be essentially the same.” The guideline allows widening of Cmax for drugs with more than 30% intra subject variability and it also allows the bioequivalence claim to be based on that wider interval. Telmisartan is a highly variable drug with more than 30% intra subject variability, as was demonstrated with study 1022. Consequently, it can be concluded, when Telmisartan test and reference product show bioequivalence as in study 1040, that the products could be considered therapeutically equivalent and should be similar in terms of efficacy and safety. The difference in Telmisartan Cmax of up to 30% can therefore be considered irrelevant in terms of efficacy and safety.

Consequently, it is the view of the CHMP that bioequivalence between the generic drug product and the brand leader has been demonstrated.

In this study, no serious or severe adverse events (AEs) were reported. Thirteen AEs were seen in 6 subjects who received Telmisartan 80 mg Tablets. Of these 13 AEs, 11 were considered to be mild and 2 were considered as moderate. These consisted of 3 events of dizziness, 2 events of headache, 2 events of coughing, 1 event of flu-like symptoms, 1 event of herpes simplex, 1 event of nausea, 1 event of vomiting, 1 event of chills and 1 event of pharyngitis. As the one instance of vomiting was judged to be unlikely to be related to the study drug, the subject was permitted to continue with the study. Four AEs were seen in 3 subjects who received Micardis 80 mg Tablets and all were considered to be mild. These consisted of 1 event of pain on arm, 1 event of rhinitis, 1 event of pharyngitis and 1 event of headache.

- Conclusions

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

## 2.4.3. Pharmacodynamics

No studies were submitted, which is acceptable.

**Post marketing experience**

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

## *2.5. Pharmacovigilance*

**Detailed Description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the applicant in version 5.03 dated 12 October 2009 presented in Module 1.8.1. of the Marketing Authorisation Application, fulfils the legislative requirements. The company must ensure that this system is in place and functioning before the product is placed 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. The next PSUR for the reference product Micardis will cover the period from 12 April 2010 to 11 April 2011 and should be provided for CHMP review no later than 60 days as of the DLP.

**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 Telmisartan Actavis 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.

**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. Benefit/risk assessment and recommendation*

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 Telmisartan Actavis 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.

Since the application contains adequate quality and clinical data and the bioequivalence has been shown, a benefit/Risk ratio comparable to the reference product can therefore be concluded. There are no new data, which would change the benefit/risk ratio of using telmisartan in general.

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.

## *2.7. Recommendation*

Based on the CHMP review of available data, the CHMP considered by consensus that the benefit/risk ratio of Telmisartan Actavis in the treatment of essential hypertension in adults and 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, was favourable and therefore recommended the granting of the marketing authorisation.