European Medicines Agency
Evaluation of Medicines for Human Use

Doc. Ref.: EMEA/729732/2009

ASSESSMENT REPORT

FOR

Irbesartan Teva

International Nonproprietary Name: **irbesartan**

Procedure No.: EMEA/H/C/001093

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 Teva Pharma B.V. submitted on 30 October 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Irbesartan Teva, 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.

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: **Aprovel**
    - Marketing authorisation holder: **Sanofi Pharma Bristol Myers Squib SNC**
    - Date of authorisation: **27 August 1997**
    - Marketing authorisation granted by:
        - **Community**
    - Community Marketing authorisation number: **EU/1/97/046/001-039**

- 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: **Aprovel**
    - Marketing authorisation holder: **Sanofi Pharma Bristol Myers Squib SNC**
    - Date of authorisation: **27 August 1997**
    - Marketing authorisation granted by:
        - **Community**
    - Community Marketing authorisation number: **EU/1/97/046/001-039**
    - Bioavailability study number: **1056**

The Rapporteur appointed by the CHMP was Concepcion Prieto Yerro

Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

Licensing status:

An application was filed in the following countries: Spain. 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 EMEA on 30 October 2008.
- The procedure started on 19 November 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 6 February 2009.
- During the meeting on 16-19 March 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 20 March 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 24 April 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 12 June 2009.
- During the CHMP meeting on 22-25 June 2009, 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 2 July 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 15 July 2009.
- During the meeting on 20-23 July 2009, 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 Irbesartan Teva on 23 July 2009.
- The CHMP opinions were forwarded in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 30 October 2009.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Irbesartan Teva 75 mg, 150 mg and 300 mg film-coated tablet is a generic medicinal product containing irbesartan as active substance. The application was submitted under the Article 10(1) of Directive 2001/83/EC i.e. generic application referring to a reference medicinal product.

Irbesartan is a potent, orally active, selective angiotensin-II receptor (type AT1) antagonist. It is expected to block all actions of angiotensin-II mediated by the AT1 receptor, regardless of the source or route of synthesis of angiotensin-II. The selective antagonism of the angiotensin-II (AT1) receptors results in increases in plasma renin levels and angiotensin-II levels, and a decrease in plasma aldosterone concentration. Serum potassium levels are not significantly affected by irbesartan alone at the recommended doses. Irbesartan does not inhibit ACE (kininase-II), an enzyme which generates angiotensin-II and also degrades bradykinin into inactive metabolites. Irbesartan does not require metabolic activation for its activity.

The efficacy and safety of irbesartan has been demonstrated in several randomised, double-blind placebo controlled studies, and controlled studies with active comparators in patients with hypertension. Irbesartan was also studied in two large studies in kidney disease in patients with type 2 diabetes. A summary of these studies can be found in the EPAR of Aprovel.

The indication proposed for irbesartan is the same as authorised for the reference medicinal product Aprovel.

2.2 Quality aspects

Introduction

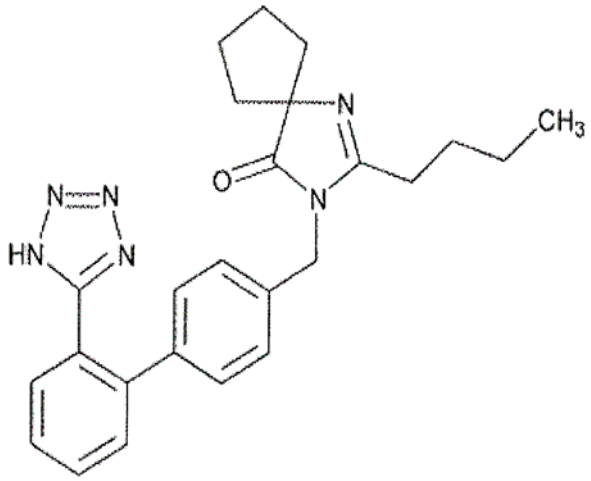
Irbesartan Teva is presented as film-coated tablets containing 75 mg, 150 mg or 300 mg of irbesartan (active substance). Excipients used in the preparation of Irbesartan Teva are well known excipients used in tablets preparations such as povidone, pregelatinized starch (maize), poloxamer 188, microcrystalline cellulose, croscarmellose sodium, silica, colloidal hydrated, magnesium stearate (present in the tablet core) and Opadry II OY-GM-28900 white (coating agent) which is composed of polydextrose (E1200), titanium dioxide (E171), hypromellose (E464) and macrogol 4000.

Irbesartan Teva film-coated tablets white to off white capsule shaped. One side of the tablet debossed with the number “93”. The other side of the tablet debossed with number “7464” (75 mg tablets), “7465” (150 mg tablets) and “7466” (300 mg tablets).

The tablets are packed in PVC/PVdC white opaque – aluminium blisters.

Active Substance

The active substance is chemically designated as 2-butyl-3-({4-[2-(2*H*-1,2,3,4-tetrazol-5-yl)phenyl]phenyl}methyl)-1,3-diazaspiro[4.4]non-1-en-4-one (IUPAC Name) or 2-butyl-3-[[4-[2-(2H-tetrazol-5-yl)phenyl]phenyl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one (Chemical name) and has the following structure:



Irbesartan is a white to off-white crystalline, non hygroscopic powder, which is sparingly soluble in alcohol and methylene chloride, practically insoluble in water.

Two crystalline polymorph forms of irbesartan are known from the literature: form A and form B. The commercially utilised manufacturing process is optimised to produce the desired polymorphic form. X-ray powder diffraction showed a consistency of the polymorphic content in various batches of irbesartan.

- Manufacture

Information about manufacturing process has been provided using Active Substance Master File (ASMF) procedure.

Critical parameters and accompanying in-process controls, to ensure quality of the final compound, have been defined.

Confirmation of the chemical structure of irbesartan was provided by spectroscopic methods as FT-IR, NMR (^{1}H-NMR and ^{13}C-NMR), mass spectroscopy and X-ray powder diffraction (XRD). The X-ray diffraction studies confirmed the proposed crystalline form.

Potential impurities have been well discussed in relation to their origin and potential carry-over into the final drug substance, including potential for the formation of genotoxic impurities.

- Specification

The drug substance specification includes tests for appearance, identification (FTIR, HPLC and XRD), water content (Karl-Fisher), heavy metals, sulphated ash, related substances (HPLC), assay (HPLC and XRD), residual solvents (GC), particle size distribution, bulk density and tapped density.

A detailed description for all analytical methods was provided. Since irbesartan is not yet described the European Pharmacopoeia the in-house test methods for the quality control of the active substance, considering European Pharmacopeia General Methods section, have been developed. Full method validation data was provided for the non compendial analytical methods: HPLC methods for identification assay, and related substance, GC method for residual solvents and XRD method for identification and quantitative determination of the polymorphic form.

The HPLC method for related substances has been validated for specificity and selectivity, linearity, limit of quantitation, limit of detection, accuracy and recovery, precision (system precision, method precision and method reproducibility), robustness, and stability of standard and sample.

The HPLC method for assay has been validated for method precision (system precision, method precision and method reproducibility), linearity and accuracy and stability of standard solution. Validation data indicates that the method is valid and fully applicable for control of irbesartan content in drug substance.

The XRD method for identification and quantitative determination of the polymorphic form also has been validated with regards to method precision (method precision and method reproducibility), linearity, accuracy and specificity.

The GC method for determination of residual solvents has been validated with respect to system precision, method precision, method reproducibility, accuracy and recovery, linearity, specificity and selectivity, limit of quantitation, robustness and stability of standard and sample solution. Validation indicates that the method is valid and fully applicable for control of residual solvents in the active substance.

In general analytical methods proposed are suitable to control the quality of the drug substance.

Data on three consecutive batches of irbesartan manufactured according to the proposed manufacturing process in the proposed manufacturing sites was provided. All batches represented full scale production and complied with the requirements in the drug substance specification.

- Stability

Stability studies were carried out according to ICH guidelines for real time (25°C/60% RH) and accelerated conditions (40°C/75% RH). Data for six batches were given with 24 and 48 months real time and 6 months accelerated data.

In addition forced degradation and photostability studies have been performed. A discussion about the potential degradation pathways of the substance based on the results from forced degradation study has been provided. Irbesartan was exposed to acidic, alkaline and oxidation, and also to the thermal treatment (heat). The photostability in solid state and in solution has been conducted and no significant changes were observed. No unknown impurities were detected during stability testing.

The stability studies confirmed the proposed re-test period.

Medicinal Product

- Pharmaceutical development

The aim of the pharmaceutical development was to obtain, a robust and stable immediate release tablet formulation containing qualitatively and quantitatively the same active substance as the reference product and which is comparable in terms of dissolution and bioequivalent with the reference product.

Similarity with the reference medicinal product was addressed by dissolution studies and comparative impurity profiles.

Compositions of Irbesartan Teva film-coated tablets and the reference product are similar.
Irbesartan Teva film-coated tablets contain microcrystalline cellulose, croscarmellose sodium, magnesium stearate, colloidal hydrated silica, pregelatinised maize starch, poloxamer 188 and povidone. The reference medicinal product was authorised through the centralised procedure and therefore the qualitative and quantitative composition of the active substance (irbesartan) and the excipients (microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, magnesium stearate, colloidal hydrated silica, hypromellose) is identical in all Member States. The formulation of Irbesartan Teva film-coated tablets differs by the inclusion of poloxamer 188 and povidone compared to lactose monohydrate and hypromellose in reference medicinal product.

Similarity between two products was also shown by dissolution testing. Comparative dissolution profiles of Irbesartan Teva 75 mg, 150 and 300 mg film-coated tablets and reference product Aprovel 75 mg, 150 mg and 300 mg film-coated tablets in three different media: 0,1 M HCl, phosphate buffer pH 4,5 and phosphate buffer pH 6,8 have been conducted. The dissolution profiles of test product and reference product are considered similar in all three media.

Impurity profile comparisons and assay values of test product and reference product showed that Irbesartan Teva and the reference product have comparable assay values and impurity profile.

A bioequivalence study was conducted, under fasting conditions, in order to prove in-vivo bioequivalence between Irbesartan Teva 300 mg film-coated tablets and the reference product Aprovel 300 mg film-coated tablets. The application concerned three strengths of 75 mg, 150 mg and 300 mg film-coated tablets however the bioequivalence was demonstrated between Irbesartan Teva 300 mg film-coated tablets and Aprovel 300 mg film-coated tablets and biowaiver for a bioequivalence study with the 75 mg and 150 mg strengths was claimed. The biowaiver could be applied since:

- all strengths are manufactured by the same manufacturer and process,
- the drug input has been shown to be linear over the therapeutic dose range (irbesartan exhibits linear and dose proportional pharmacokinetics over the dose range of 10 mg to 600 mg),
- the qualitative composition of the strengths is the same,
- the ratio between amounts of active substance and excipients is the same,
- the dissolution profiles were similar for all and the tablets are rapidly dissolved products (more than 85% of the labelled amount dissolved after 15 minutes).

The drug product manufacturing process development was also performed. Details were provided for experimental batches manufactured to establish optimum manufacturing conditions. To obtain immediate release tablets, which were essentially similar to the reference product, a formulating strategy was undertaken in order to optimize the manufacturing process. A common formulation and manufacturing process was developed for all strengths. Due to high percentage of the drug substance in the formulation, a wet granulation process was selected.

- Adventitious Agents

None of the excipients used in the drug product is of human or animal origin. Magnesium stearate used in the formulation is of vegetal origin.

- Manufacture of the Product

The proposed manufacturing process is a standard process utilised in tablet manufacture and consists of several steps including premixing, wet granulation, drying and milling, mixing of blend, compression (tabletting) of the final blend, film-coating and packaging.

The process has been sufficiently characterized. Critical steps (granulation, tabletting and coating) and in-process controls have been identified. A flow diagram and detailed description of the manufacturing process have been provided.

Process validation data were provided for two pilot scale batches of each tablet strength. In addition the validation protocol has been provided and the applicant committed that full process validation will be performed on three consecutive commercial batches.

- Product Specification

The product specification is a standard one for tablets and contains tests with suitable limits for appearance, identification (HPLC and UV), uniformity of dosage units by mass variation, water content (Karl-Fisher), thickness of cores, friability of uncoated tablets, resistance to crushing of

tablets, assay (HPLC), impurities and degradation products (HPLC), dissolution, microbial limits and identification of colouring agent (titanium dioxide).

Full details of all analytical methods have been provided. All non pharmacopoeial methods have been satisfactory validated.

The HPLC methods for assay and related substances have been suitably validated with respect to intermediate precision, method precision, accuracy and recovery, linearity, specificity and selectivity (degradation peaks are well separated from the main peak), limit of quantitation, stability of samples and standard solutions and robustness. Validation results indicate that the method is suitable for evaluation of assay and for control of related substances in drug product.

The UV method for evaluation of dissolved irbesartan has been validated with respect to intermediate precision, method precision (repeatability), accuracy (by comparing results with the results obtained for the same samples using the HPLC method), linearity, specificity and selectivity, standard and sample solution stability and robustness of the method.

Batch analysis data was provided on six pilot scale batches of the finished product (2 batches for each strength). Results demonstrate compliance with the proposed specification and confirm consistency and uniformity of the product. It has been shown that tablets can be manufactured reproducibly according to the finished product specifications.

- Stability of the Product

Stability studies under ICH conditions of 25ºC/60%RH (long term, 12 months) and 40ºC/75%RH (accelerated, 6 months) were carried out on two pilot scale batches of each strength. Containers used in the stability studies were the same as those proposed for commercialisation.

Photostability studies have also been included in the stability program. No significant differences in irbesartan assay and degradation products content were observed. In conclusion, Irbesartan Teva film-coated tablets are considered photostable.

Stability results showed no increase of the impurities (known and unknown). The results are well within the specifications. Based on the stability data the proposed shelf-life and storage conditions as defined in the SPC are acceptable.

In summary the stability data provided support the proposed shelf-life and storage conditions.

Discussion on chemical, and pharmaceutical aspects

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

Irbesartan is widely used well-known substance. Its pharmacodynamic, pharmacokinetic and toxicological properties are well characterised. No further studies are required and the applicant has justified why no such data were provided.

The environmental risk assessment (ERA) in line with the CHMP Guideline on Environmental Risk Assessment of Medicinal Products for Human Use (CPMP/SWP/4447/00) was not submitted; however, a justification for omission of environmental risk assessment was provided. This was based on the fact the generic medicinal product is intended to substitute the reference product and it will not result in additional hazard to the environment. The supplied justification for the lack of a full ERA was considered acceptable by the CHMP.

2.4 Clinical Aspects

Introduction

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

GCP

The bioequivalence study is stated to have been performed in accordance with GCP and the ethical requirements of Directive 2001/20.

The clinical part of the study was performed by a CRO in Canada. The Clinical Laboratory and the Analytical centre were both located in Canada. The Pharmacokinetic, Statistical and Report Issuing Facility was another CRO located in Canada.

The applicant has clarified that the clinical centre has been inspected by Regulatory Agencies in 2008, including FDA (USA) and Health Canada. The FDA has also inspected the analytical site.
The outcome of these inspections was assessed during the procedure and considered satisfactory.

Clinical study

To support the application, the applicant has submitted a single-dose, fasted-state bioequivalence study.

Pharmacokinetics

- Methods

STUDY DESIGN

Single-Dose, Randomized, Open-Label, Three-Way Crossover, Comparative Bioavailability Study of Two Formulations of Irbesartan 300 mg Tablets (Teva Pharmaceutical Industries Ltd.) and Aprovel™ 300 mg Film-Coated Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France) in Normal, Healthy Subjects under Fasting Conditions.

Subjects who met the eligibility criteria were randomly assigned to receive the study drugs according to one of the three dosing sequences A-B-C, B-C-A, or C-A-B. A total of 8 subjects were planned to receive treatment sequence A-B-C, 8 subjects were planned to receive sequence B-C-A, and 8 subjects were planned to receive sequence C-A-B. The washout period was a minimum of 7 days between each dosing, but no more than 14 days.

Subjects took their assigned study medication, designated by the randomization scheme, after a 10-hour fast, with 240 mL of ambient temperature water at their scheduled timepoint. Blood samples were taken at the following time points: pre-dose and at 0.25, 0.5, 0.67, 0.83, 1.0, 1.25, 1.5, 1.75, 2.0, 2.33, 2.67, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 hours after dosing.

The protocol (version date 09/01/2008) and informed consent forms (ICFs) (version date 08/01/2008) were reviewed and approved by an Institutional Review Board (IRB). Following changes to the existing Protocol and ICF, new versions were approved on February 01, 2008.
The clinical phases were performed the 03/02/2008, 10/02/2008 and 13/02/2008.
The analysis of the samples was conducted on the period from 26/02/2008 to 08/03/2008.

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

TEST AND REFERENCE PRODUCTS

Treatment A: Irbesartan 300 mg film-coated tablets EU; Lot No: K-39692; (Teva Pharmaceutical Industries Ltd.)

Treatment B: Irbesartan 300 mg film-coated tablets EU; Lot No: K-39693; (Teva Pharmaceutical Industries Ltd.).

Treatment C: Aprovel™ 300 mg film-coated tablets; Lot No: 2165; (Sanofi Pharma Bristol-Myers Squibb SNC, France). Expiry date: 02/2009

Biowaiver

According to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence *CPMP/EWP/QWP/1401/98* a bioequivalence study investigating only one strength may be acceptable if a new application concerns several strengths of the active substance. However the choice of the strength used should be justified on analytical, pharmacokinetic and safety grounds. The selection of the dose has been done according to the recommended doses normally administered to patients (respecting the therapeutic range), and in order to obtain measurable plasma concentrations after administration.

Furthermore all of the following conditions should be fulfilled:

- the pharmaceutical products are manufactured by the same manufacturer and process,
- the drug input has been shown to be linear over the therapeutic range (if this is not the case the strengths where the sensitivity is largest to identify differences in the two products should be used),
- the qualitative compositions of the different strengths is the same,
- the ratio between amounts of active substance and excipients is the same, or, in the case of preparations containing a low concentration of the active substance (less than 5%), the ratio between the amounts of excipients is similar,
- the dissolution profile should be similar under identical conditions for the additional strength and strength of the batch used in bioequivalence study.

All the above points were met. Dissolution tests were performed at pH 1.2, 4.5 and 6.8 in paddle apparatus, 50 rpm, in 1000 ml of dissolution media. Dissolution was complete at pH 1.2. The values at 15 minutes were higher than 85% and therefore the dissolution profiles are similar. At pH 4.5 dissolution was minimal (<10%) in all strengths. And at pH 6.8 dissolution was almost complete, but the dissolution of the highest strengths is slightly slower than with the other lower strengths because of the lack of sink conditions. This behaviour is acceptable since it occurs similarly in the reference product.

It is also important to highlight that Poloxamer 188 is not a conventional excipient in tablets. However, as bioequivalence has been shown with the highest strength and dose, it can be assumed that lower amounts included in the proportional formulations will not affect negatively the bioavailability of the drug.

POPULATION STUDIED

Twenty-four (24) subjects were enrolled in the study. One subject was dismissed by the Investigator due to an adverse event and the use of concomitant medication. Data from this subject were excluded from the pharmacokinetic and statistical analysis. Additionally, two subjects voluntarily withdrew for personal reasons after having completed 2 periods of the study, resulting in the administration of at least one test product and the reference product. Data from these subjects were included in the pharmacokinetic and statistical analysis. Thus, a total of twenty-three (23) subjects were included in the final data set and therefore in the pharmacokinetic and statistical analyses.
Subjects who withdrew or were dismissed due to adverse events were not replaced.

ANALYTICAL METHODS

A method for determining irbesartan in human plasma has been validated using LC/MS/MS system.

This analytical method is able to distinguish the parent drug from the major circulating metabolite (inactive irbesartan glucuronide).

The validation of the analytical method is satisfactory.

Pre-study validation
For irbesartan, the overall inter-day precision (%CV) and accuracy (%Bias) for the standards and quality control samples was within an acceptable.
The interference checks due to common medications such as acetaminophen, aspirin, chlorpheniramine maleate and ibuprofen, as well as caffeine, were evaluated under irbesartan assay conditions. The results showed no interference observed at the retention time of irbesartan or the internal standard.

In-study validation
Inter-day precision (%CV) and accuracy were determined.
For irbesartan standards, a single calibration curve was analyzed with each batch run.
For sample analysis, each batch run consisted of standards in singlet and QC samples at least in duplicate.

PHARMACOKINETIC VARIABLES

Standard pharmacokinetic variables were determined through non-compartmental analysis by the linear trapezoidal rule. The pharmacokinetic analysis was performed using SAS® Version 9.1 or higher.

STATISTICAL METHODS

ANOVA was performed on the natural logarithm-transformed data for AUC_t, AUC_{inf}, and C_{max} and on the raw data for AUC_t, AUC_{inf}, C_{max}, T_{max}, λ and $T_{1/2}$. T_{max} was compared between Test and Reference products using an additional non-parametric method. The significance of the sequence, subjects nested within sequence, period and treatment were tested.
The 90% confidence intervals (CI) of the Test/Reference ratios of geometric means for AUC_t, AUC_{inf}, and C_{max} were calculated based on the least square means (LSMEANS) and estimate of the ANOVA.
The statistical analysis was performed using SAS® Version 9.1 or higher.

- Results

Based on the statistical analysis the test products are equivalent to the reference with respect to the extent and rate of absorption / exposure. The 90% confidence intervals calculated for $AUC_{(0-t)}$, $AUC_{(0-inf)}$ and C_{max} of irbesartan were inside the normal range of acceptability (0.80 – 1.25) (see Table 1 below). However, these calculations were at first considered not valid due to a controversial decision on the exclusion of one subject and the inclusion of two subjects (see section “Population studied”) and the unjustified exclusion of some AUC values from subjects included in the dataset. This concern was raised as a major objection by the CHMP who required the submission of additional calculations as sensitivity analysis to confirm the bioequivalence of the formulation. Two additional sets of analyses were carried out (with n=21 and n=24) and the sensitivity analysis showed bioequivalence in all cases. Therefore the conclusion of bioequivalence was considered robust and not influenced by the number of subjects excluded from statistical analysis.

Table 1

Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} ,median, range)

Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)
	TRT A	TRT C		
AUC_t (ng*h/mL)	15150.584 16365.760 (38.69) N = 21	15772.686 17043.475 (36.67) N = 22	0.9606	0.8949 – 1.0310
AUC_{inf} (ng*h/mL)	15621.135 16666.571 (38.06) N = 21	16129.882 17278.307 (36.62) N = 22	0.9685	0.9050 – 1.0364
C_{max} (ng/mL)	3481.965 3621.227 (28.71) N = 22	3226.302 3404.522 (32.88) N = 23	1.0792	0.9833 – 1.1846
T_{max}[a] (h)	0.92 (0.50 – 5.00) N = 22	1.00 (0.50 – 5.00) N = 23		
λ[b] (1/h)	0.0765 (43.27) N = 21	0.0824 (35.04) N = 22		
$T_{1/2}$[b] (h)	10.77 (40.55) N = 21	9.23 (28.96) N = 22		
AUC_t/AUC_{inf}[b]	0.9796 (2.04) N = 21	0.9861 (0.78) N = 22		
Parameter	**Geometric Means Arithmetic Means (CV%)**		**Ratio of Geometric Means (%)**	**90% Confidence Interval (%)**
	TRT B	**TRT C**		
AUC_t (ng*h/mL)	15167.382 16645.505 (38.75) N = 21	15772.686 17043.475 (36.67) N = 22	0.9616	0.8959 – 1.0322
AUC_{inf} (ng*h/mL)	15572.859 17099.285 (38.53) N = 20	16129.882 17278.307 (36.62) N = 22	0.9655	0.9000 – 1.0357
C_{max} (ng/mL)	3321.035 3624.727 (45.35) N = 22	3226.302 3404.522 (32.88) N = 23	1.0294	0.9376 – 1.1302
T_{max}[a] (h)	1.50 (0.50 – 5.02) N = 22	1.00 (0.50 – 5.00) N = 23		
λ[b] (1/h)	0.0761 (44.12) N = 20	0.0824 (35.04) N = 22		
$T_{1/2}$[b] (h)	10.80 (44.19) N = 20	9.23 (28.96) N = 22		
AUC_t/AUC_{inf}[b]	0.9836 (1.01) N = 20	0.9861 (0.78) N = 22		

TRT A: Irbesartan 300 mg Tablets EU; Lot No: K-39692; (Teva Pharmaceutical Industries Ltd.)
TRT B: Irbesartan 300 mg Tablets EU; Lot No: K-39693; (Teva Pharmaceutical Industries Ltd.)
TRT C: Aprovel™ 300 mg Tablets; Lot No: 2165; (Sanofi Pharma Bristol-Myers Squibb SNC, France)

[a] Presented as median and range
[b] Presented as arithmetic mean (CV%) only

Protocol deviations:

One subject failed to disclose his full medical history at screening and was included in the study. This subject was dismissed from the study for an adverse event and for use of concomitant medication. The subject's data was excluded from the pharmacokinetic and statistical analyses but this decision was considered controversial by the CHMP and new analyses including these data were provided by the applicant during the procedure (see section "Population studied")

Another subject had an unknown actual collection time for the 48 hours time points. However, this sample was treated as collected on time.

There were also a significant number of deviations in the sampling times with respect to the schedule time point. Sampling times were adjusted using the blood sampling time deviations in the pharmacokinetic analysis in order to more accurately reflect the temporal collection of samples.

These deviations were considered normal and acceptable by the CHMP since they did not have any impact on the study results.

Safety data:

There were 8 adverse events involving 5 subjects in this study.
A total of 2 mild AEs (somnolence and pain in extremity) were experienced by the subjects after taking Treatment A (Test product) and 2 mild AEs (oral herpes and contusion) were experienced by the subjects after taking Treatment B (Test product). A total of 4 mild AEs (pain in extremity, somnolence and headache) were experienced by the subjects after taking Treatment C (Reference product). All these adverse events were considered unrelated to the treatment. No serious adverse events were reported during the conduct of this study. The test and reference products were well tolerated by all subjects.

The safety profile of both products seems to be comparable although the design was not powered to compare the safety profile. At this point in time, no difference in the safety profile is anticipated.

- Conclusions

Based on the presented bioequivalence study Irbesartan Teva is considered bioequivalent with Aprovel.

The results of the study with the 300 mg formulation can be extrapolated to other strengths 75 mg and 150 mg, according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

Pharmacodynamics

No studies were submitted.

Post marketing experience

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

2.5 Pharmacovigilance

- **PSUR**

The PSUR submission schedule should follow the PSUR schedule for the reference product.

- **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 7.0 date 28 May 2009 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

- **Risk Management Plan**

No description of Risk Management Plan has been provided by the applicant. Since the application concerns a generic with a reference medicinal product for which no safety concerns requiring additional risk minimisation activities have been identified, this approach is considered acceptable.

Discussion on Clinical aspects

Bioequivalence between the test product and the reference product has been shown for the 300 mg strength. However, the exclusion of some subjects and some AUC values of included subjects was raised as a major objection by the CHMP. In response, the applicant submitted two additional sets of analyses and the sensitivity analysis showed bioequivalence in all cases.
The conclusion of bioequivalence was therefore considered robust by the CHMP.

Extrapolation of this evidence to the proportional strengths of 75 and 150 mg is possible since bioequivalence has been shown with the highest strength and kinetics is linear, the different strengths are qualitatively identical and quantitatively proportional in composition and dissolution profiles have shown to be sufficiently similar at pH 1.2, 4.5 and 6.8.

2.6 Overall conclusions, benefit/risk assessment and recommendation

Overall conclusion and Benefit/risk assessment

The application contains adequate quality, non clinical and clinical data and the bioequivalence has been shown. A benefit/Risk ratio comparable to the reference product can therefore be concluded.

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.

Recommendation

Based on the CHMP review of available data, the CHMP considered by consensus decision that the benefit/risk ratio of Irbesartan Teva in the treatment of essential hypertension and treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive drug regimen was favourable and therefore recommended the granting of the marketing authorisation.