European Medicines Agency
Evaluation of Medicines for Human Use

ASSESMENT REPORT

FOR

Irbesartan / Hydrochlorothiazide Teva

International Nonproprietary Names: Irbesartan / Hydrochlorothiazide

Procedure No. EMEA/H/C/001112

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

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 45
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Teva Pharma B.V submitted on 03 December 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Irbesartan/Hydrochlorothiazide 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 2007/83/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(s), pharmaceutical form(s): CoAprovel 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg tablets
    - Marketing authorisation holder: Sanofi Pharma Bristol-Myers Squibb SNC
    - Date of authorisation: 1998-10-15
    - Marketing authorisation granted by: Community
      Marketing authorisation numbers: EU/1/98/086/001-034

- *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(s), pharmaceutical form(s):CoAprovel 150 mg/12.5 mg tablets and 300 mg/12.5 mg tablets
    - Marketing authorisation holder4: Sanofi Pharma Bristol-Myers Squibb SNC
    - Date of authorisation: 1998-10-15
    - Marketing authorisation(s) granted by: Community
      Marketing authorisation numbers: EU/1/98/086/001-022, EU/1/98/086/0029-30, EU/1/98/086/0032-33

The Rapporteur appointed by the CHMP was Concepción Prieto Yerro

Scientific Advice:

Not applicable

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 EMEA on 08 December 2008.
- The procedure started on 24 December 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 20 March 2009 .
- During the meeting from 20 - 23 April 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 23 April 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 May 2009.
- The Rapporteur circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 09 July 2009.
- During the CHMP meeting on 20 – 23 July 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 consolidated List of Outstanding Issues on 24 August 2009.
- During the meeting from 21 - 24 September 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/Hydrochlorothiazide Teva on 24 September 2009.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Teva Pharma has applied for a marketing authorisation via the centralized procedure for Irbesartan/Hydrochlorothiazide Teva, a generic medicinal product of a reference medicinal product authorised by the Community in accordance with Regulation EC 726/2004 article 3.3. The reference product for this generic application is CoAprovel 150/12.5; 300/12.5; 300/25 mg film coated tablets (Sanofi Pharma Bristol-Myers Squibb SNC, Germany), registration number EU/1/98/001-034 date of registration: 15.10.1998.
For one bioequivalence study (in vivo), Irbesartan/Hydrochlorothiazide 300/12.5 mg film coated tablets (Teva) has been used and as reference product CoAprovel 300/12.5 mg film-coated tablets (Sanofi Pharma Bristol-Myers Squibb). For another study, Irbesartan/Hydrochlorothiazide 150/12.5 mg film coated tablets (Teva) has been used and as reference product CoAprovel 150/12.5 mg film-coated tablets (Sanofi Pharma Bristol-Myers Squibb).
Irbesartan/Hydrochlorothiazide Teva is a combination of an angiotensin II receptor blocker and a thiazide diuretic, which is indicated for the treatment of hypertension.
In general doses higher that 300 mg irbesartan/ 25 mg hydrochlorothiazide once daily are not recommended.

2.2 Quality aspects

Introduction

Irbesartan / Hydrochlorothiazide Teva is presented as film-coated tablets 150/12.5 mg, 300/12.5 mg and 300/25 mg of irbesartan and hydrochlorothiazide respectively. The 150/12.5 mg and 300/12.5 mg strengths are light pink to pink capsule-shaped, film-coated tablets and the 300/25 mg strength is pink to dark pink capsule-shaped, film-coated tablets. They contain both active substances irbesartan and hydrochlorothiazide.
Excipients used in the preparation of the core tablets Irbesartan Hydrochlorothiazide Teva are well known excipients used in solid dosage forms such as povidone, starch, pregelatinised, poloxamer 188, cellulose microcrystalline, croscarmellose sodium, silica colloidal anhydrous, magnesium stearate.

The tablets are packed in (PVC/PVdC white opaque/ Al) blister and Aluminium/Aluminium blisters.

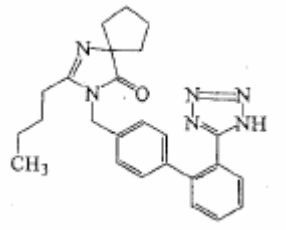
Active Substance

IRBESARTAN

Irbesartan (INN) is an active substance only described in USP pharmacopoeia.

The applicant has used the Active Substance Master File (ASMF) procedure and including the open part and the restricted part as well as a letter of authorisation from the ASMF holder

The structural formula of Irbesartan is provided below and general properties such as appearance, melting point, solubility, partition coefficient and water content have been adequately detailed.



Irbesartan is obtained by chemical synthesis to yield a purified active substance. The manufacturing process is adequately described. Information related to the control of materials, intermediates, process development and validation can be found in the restricted part of the ASMF and were found satisfactory.

Studies were conducted for elucidating the structure of Irbesartan using the following techniques: Infrared spectrophotometry (FTIR), Nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR) spectroscopy, Mass spectrometry. The physico-chemical studies including hygroscopicity and polymorphism were presented and the synthesis support unequivocally the proposed chemical structure. The copy of the spectra and interpretation of results were included.
Irbesartan is not hygroscopic and regarding polymorphism, two crystal forms of Irbesartan are described in the literature: form A and form B. Teva consistently produces one form. The X-Ray Diffractometry analyses (XRD) showed the consistency of the polymorphic content in various batches.
An extensive discussion on the impurities (inorganic, organic and residual solvents) was enclosed including their characterisation when necessary. Impurities level was adequately controlled and below qualification limits, and in accordance with the European and ICH guidelines. In particular for the residual solvents, limits were below the ICH Q3C Guidance and European Pharmacopoeia requirements.

Correct specifications were proposed for Irbesartan by Teva and included the following parameters: description (visual), identification (FT-IR and HPLC, XRD), water content (Karl Fischer), heavy metals content (PhEur.), sulphated ash (PhEur.), related substances (HPLC), assay (HPLC), residual solvents (GC).

Since Irbesartan is not yet described in the official European Pharmacopoeia. Teva has developed its own test methods for the quality control of the active substance, following European Pharmacopeia General Methods section. The methods used for the quality control of active substance are appropriate to guarantee the relevant quality from batch to batch.
All the validation studies were found acceptable and followed the ICH-guideline "Validation of Analytical Procedures"ICH Q2R1.

A total of 6 production-scale batches of Irbesartan from the different manufacturers were obtained and results were in line with the proposed specification.

The active substance is filled into double aluminium laminate bags, placed in a closed HDPE container. The primary packaging (aluminium bag) has been adequately analysed and certificates of analysis provided.

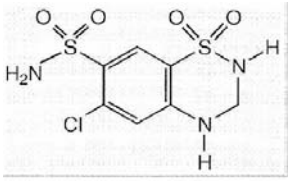
Stability studies under various conditions (forced degradation studies, photostability studies, long term and accelerated studies) have been carried out by the applicant on Irbesartan.
According to CPMP/QWP/122/02 rev1 corr the applicant submitted a discussion about the potential degradation pathways of the substance under forced degradation studies.
The photostability studies indicated that the active substance was not light sensitive when in the solid state but would be when in solution.

Formal stability studies were conducted on production batches kept in double aluminium laminate bags under ICH conditions (up to 24 months at 25C/60% RH and 6 months at 40C/75%RH).
The following parameters were studied: description, identification (HPLC), water content, related substances and assay. Those tests are stability indicating. Data to confirm that the polymorphic form of the API is maintained during stability have been provided.
No significant changes could be observed under accelerated and long term stability conditions.
The stability studies support the proposed re-test period of the active substance when kept in the commercial packaging. No special condition of storage is necessary.

None of the starting materials used for the manufacture of irbesartan contain materials or have been in contact with materials of animal or human origin, during their manufacture. Therefore no TSE risk is anticipated.

HYDROCHLOROTHIAZIDE

For this active substance Hydrochlorothiazide (INN), a Certificate of suitability to the monograph of European Pharmacopeia (CEP) has been provided.



General properties have been satisfactorily described (appearance, solubility and polymorphism). Although Hydrochlorothiazide shows polymorphism, the manufacturer Teva consistently produces only one polymorphic form. The polymorphic form of hydrochlorothiazide is maintained during stability studies.

For both active substances, particle size distribution, bulk and tapped density were set according to customer request and needs, and are part of the specifications set for the Company's customers. Adequate specifications and batch analysis were provided for 4 batches of Irbesartan and 2 batches of Hydrochlorothiazide.

Medicinal Product

Pharmaceutical Development

Choice of the active substances: Particle size and polymorphism are very important parameters for Irbesartan due to its low solubility. The polymorphic form is maintained during manufacturing and stability of the medicinal product. Concerning the particle size adequate limits have been chosen.
Hydrochlorothiazide is a highly water soluble drug so neither polymorphism nor particle size distribution can affect the quality or performance of the finish product.
This (particle size and polymorphism) was extensively discussed and limits were fully justified.

Choice of the excipients: they are all standard and are commonly used for solid oral dosage forms. These are expected to be chemically compatible with irbesartan and hydrochlorothiazide.
Excipients chosen were selected to provide an optimal solubility and stability of the active substance during manufacturing and storage. The ability of these excipients to provide their intender functionality is well-known.

The aim of the pharmaceutical development was to obtain an immediate-release tablet containing qualitatively and quantitatively the same active substance as the product already on the market CoAprovel film coated tablets.

Manufacturing process development: Due to the high percentage of the active substances in the formulation, wet granulation process was selected.

Container closure systems selected were: PVC/PVdC-aluminium blister packs and Aluminium-aluminium blister packs. Specifications and certificates of analysis for PVC/PVdC film and aluminium foil were provided. The quality of these materials are correctly defined and the suitability of these containers have been justified by stability data

Manufacturing process

The manufacturing process can be divided in 9 main steps. The process can be summarised as follow: Premixing, Granulation, Drying and Milling, Mixing of blend, Final blend, Compression, Coating and Packaging
Adequate in-process controls and control of intermediates were set up.
Process validation***:*** The manufactured process is a standard process. The validation has been carried out on 2 pilot-scale batches of each strength according to CPMP/QWP/848/96 guideline. Results were satisfactory and should ensure a consistent manufacture of the medicinal product. Furthermore the process validation schemes for commercial batch sizes proposed of the medicinal product have been submitted.

The compendial excipients used in the film-coated tablets are described as follow along with their role: povidone (binder), starch, pregelatinised (binder-disintegrant), poloxamer 188 (surfactant-solubilising agent), cellulose microcrystalline (diluent- disintegrant), croscarmellose sodium (disintegrant), silica colloidal anhydrous (glidant-antiadherent), magnesium stearate (lubricant).

For the film-coatings the ingredients are: titanium oxide E171 (opacifier), hypromellose 2910 (film-former), macrogol 6000 and 400 (plasticiser), iron oxides E172 red yellow and black (colorants),

indigotine E132 (colorant). They are all PhEur. excipients apart from the colorants that are described in internal monographs but comply with the latest directive amended EC Directive on colorants.
Certificates of analysis of the excipients have been submitted.
None of the excipients used for the manufacture contain materials and have been in contact with materials of animal or human origin during their manufacture.

Specifications of the medicinal product
Appropriate and justified specifications have been set for all the dosage strengths and the following parameters have been included: description (visual), identification (PDA and HPLC), dissolution (HPLC), uniformity of dosage unit (content uniformity by HPLC), thickness, hardness (PhEur.), friability (PhEur.), assay for each active substance (HPLC), related substances (HPLC), microbial quality (PhEur.), water content (Karl Fischer).
All the analytical methods were described satisfactorily and validated in line with the ICH-guideline "Validation of Analytical Procedures"ICH Q2R1.

Analysis for six pilot-scale batches of medicinal product (2 pilot batches for each strength) were provided. All batches were in compliance with the proposed specification.

Specifications and certificates of analysis (including IR spectrum) for the packaging material used for the storage of bulk tablets are provided. Stability results showed that this packaging material was suitable.

Stability
Formal stability studies have been conducted on the bulk product and the product in its commercial packaging.
Bulk stability studies were carried out for each strength. Results meet the specifications.

The stability study of Irbesartan/Hydrochlorothiazide medicinal product was performed on pilot-scale batches under ICH conditions (36 months at 25C/60% RH, 12 months at 30C/65% RH, 6 months at 40C/75% RH) kept in both packagings and according to the EMEA guideline CPMP/QWP/122/02 rev 1 corr.
Analytical methods used are those used for the quality control of the medicinal product.
The following criteria were controlled: appearance, water content, related substances, assay, dissolution, microbial quality.
Photostability of the product was confirmed.
No significant change could be observed during stability studies and therefore the results support the shelf life and storage conditions as defined in the SPC for each strength of Irbesartan/Hydrochlorothiazide 150/12.5. 300/12.5 and 300/25 mg film coated tablets packed in either white opaque PVC/PVdC-aluminium blisters or in aluminium-aluminium blisters.

Discussion on chemical, and pharmaceutical aspects
Information on development, manufacture and control of the active substances Irbesartan and Hydrochlorothiazide and medicinal 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

The level of impurities found in Irbesartan/Hydrochlorothiazide Teva film-coated tablets are in line with ICH Topic Q3 requirements.

Since Irbesartan/Hydrochlorothiazide Teva is essentially similar product to reference product, no additional safety and toxicology studies were considered necessary.

No ERA has been submitted and the Applicant has presented a justification. It is accepted that the introduction of Irbesartan/Hydrochlorothiazide Teva is unlikely to result in any significant increase in the combined sales volumes for all Irbesartan/Hydrochlorothiazide containing products. The risk of an environmental impact from the use of Irbesartan/Hydrochlorothiazide is of no concern.

2.4 Clinical Aspects

Introduction

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

GCP

It is stated that all clinical work has been conducted in compliance with Good Clinical Practices (GCP) as referenced in the ICH guidelines (ICH E6), local regulatory requirements, and the principles enunciated in the Declaration of Helsinki.
Both studies were carried out in the clinical and analytical facilities of a CRO in Canada. These facilities have been inspected by European Regulatory Agencies as well as by inspections from the French (AFSSAPS) and Portuguese (INFARMED) Agencies in addition to ANVISA, FDA and HPFB. This is considered sufficient demonstration of the reliability of the study taking into account that no concern on this respect has been observed during the study assessment.

Clinical studies

This application is a generic application, therefore, demonstration of therapeutic equivalence is shown by means of pharmacokinetic bioavailability studies. New clinical studies are neither required nor submitted. Bioequivalence between the test product and the reference product has been shown in two cross-over studies after a single dose in fasting conditions of the 150/12.5 mg film coated tablet and the 300/12.5 mg film-coated tablet. A waiver for the 300/25 mg strength is applied based on the bioequivalence results and dissolution profiles obtained with the proportional strength of 150/12.5 mg since both formulations are manufactured in the same plant with the same process and the kinetics of both drugs is linear.

Pharmacokinetics

Study for the 150/12.5 mg strength

Methods

Study was a randomized, open-label, 2-way crossover, bioequivalence study of irbesartan/HCT 150/12.5 mg tablet and CoAprovel (reference) following a 150/12.5 mg dose in healthy subjects under fasting conditions. Blood samples for irbesartan and HCT were each drawn into blood collection tubes containing EDTA K2 prior to drug administration and at 0.33, 0.67, 1.00, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, and 48 hours post-dose in each period. For irbesartan only additional sample was obtained 72 hours post-dose. The treatment phases were separated by a washout period of 7 days.

This study was performed by a qualified investigator in the clinical facility of the CRO.

The clinical study protocol (dated 02/02/2007) was approved by the Ethics Committee on 15/02/2007. Amended study protocol 1 (dated 10/04/2007) was approved by the Ethics Committee on 17/04/2007. The clinical phase was performed in two groups. Subjects of group 1 were tested between 23/03/2007 and 03/04/2007. Subjects of group 2 were dosed between 14/05/2007 and 25/05/2007
The analysis of the samples was conducted in the period from 02/07/2007 to 18/07/2007.

Test and reference products

Treatment A: irbesartan/hydrochlorothiazide 150/12.5 mg film-coated tablets. Teva Pharmaceuticals Industries Ltd., Israel. Manufacture Date: Jan. 28 2007.
Treatment B: CoAprovel (irbesartan/hydrochlorothiazide), Sanofi Winthrop Industrie, France
Expiration date: 01/2009.

Population studied

Fifty-six subjects were included in the study. All 56 subjects received at least one dose of the study medication and, therefore, comprised the safety population. Fifty-three individuals who completed both treatment periods were included in the pharmacokinetic analyses. After period 1 one subject was withdrawn due to adverse events and two subjects withdrew consent for personal reasons. These subjects were not replaced. One subject was excluded from the pharmacokinetic and statistical analysis involving AUC_{0-t} due to lack of appropriate samples. As per CHMP request applicant demonstrated that bioequivalence criteria are still met after inclusion of this patient into analysis.

Analytical method

A high performance liquid chromatographic method for determination of both irbesartan and hydrochlorothiazide in human EDTA K2 plasma was used in this study.

A total of 2131 study samples were analyzed and 22 repeat analyses (1.03 %) corresponding to 22 study samples were performed. Two samples were reanalysed because of unacceptable internal standard response, 13 samples were reanalysed due to the internal standard response being lower than or equal to 5% of the mean internal standard responses and 7 samples because sample concentration being above upper limit of quantitation.

A total of 2028 study samples were analyzed and 111 repeat analyses (5.47 %) corresponding to 111 study samples were performed. Twenty-nine samples were reanalysed because of unacceptable internal standard response, 3 samples were reanalysed due to the internal standard response being lower than or equal to 5% of the mean internal standard responses, 2 samples because sample concentration being above upper limit of quantitation and 77 samples because sample concentration being above or below modified calibration range.

The validation of the analytical method is satisfactory.

Pharmacokinetic variables

Standard pharmacokinetic parameters were calculated through non-compartmental analyses of pharmacokinetic parameters and statistical analyses using Bioequiv (release 3.50), a proprietary software developed and tested for bioequivalence studies.

Statistical methods

For both irbesartan and hydrochlorothiazide, analysis of variance was performed on the ln-transformed data of AUC0-t, AUC0-inf and C_{max}. ANOVA was also carried out on the untransformed data of T1/2 el and K_{el}. A conventional statistical analysis was performed with the model including sequence, subject within sequence, period and treatment as factors. The sequence effect was tested using subjects within sequence effect as the error term. The treatment and period effects were tested against the residual mean square error.
Criteria for bioequivalence for irbesartan and hydrochlorothiazide were 90% geometric CI of the ratio of least-squares in means from the ANOVA of the ln-transformed AUC_{0-t} and C_{max} should be within 80% to 125%.

Results

All pre-dose samples were found to be below the LLOQ for both drugs.
For irbesartan T_{max} median was 1.33 h for test and 1.33 h for reference. For hydrochlorothiazide T_{max} was 1.67 for the test and 2.00 for the reference. The non-parametric analysis of T_{max} shows no-statistical significant difference in both cases. The non-parametric 90% CI has not been provided.
Only one profile for irbesartan showed C_{max} in the first sampling time (0.33 h).
For irbesartan the minimum C_{max} value was 1173.36 ng/mL and the maximum C_{max} value was 9563.18 ng/mL. For hydrochlorothoazide the minimum C_{max} value was 27.89 ng/mL and the maximum C_{max} value was 163.94 ng/mL
No statistically significant difference ($\alpha = 0.05$) was detected between the periods or the sequences for the primary variables of the study (C_{max}, AUCt).

SUMMARY OF RESULTS
IRBESARTAN
N = 53

Pharmacokinetic Parameters

Parameters		Test (Irbesartan-HCTZ (A)) Mean	SD	CV (%)	Reference (Coaprovel (B)) Mean	SD	CV (%)
AUC_{0-t}**	(ng·h/mL)	12746.73	9554.75	74.96	12500.26	7090.02	56.72
AUC_{0-inf}***	(ng·h/mL)	13810.04	10373.82	75.12	13525.20	8121.46	60.05
C_{max}	(ng/mL)	2893.04	1272.23	43.98	2604.25	868.65	33.36
Residual area***	(%)	7.09	5.70	80.34	6.22	4.30	69.21
T_{max}	(h)	1.47	0.94	64.29	1.46	0.94	64.61
T_{max}*	(h)	1.33	0.67	-	1.33	0.67	-
K_{el}***	(h^{-1})	0.0626	0.0261	41.68	0.0635	0.0265	41.82
$T_{½ el}$***	(h)	13.47	6.58	48.86	13.42	6.98	51.99

* Medians and interquartile ranges are presented.
** For these parameters, N = 52.
*** For these parameters, N = 51.

Irbesartan-HCTZ (A) vs Coaprovel (B)

	AUC_{0-t}*	AUC_{0-inf}**	C_{max}
Ratio[1]	99.69%	100.19%	107.93%
90 % Geometric C.I.[2]	96.35 % to 103.15 %	97.13 % to 103.35 %	100.75 % to 115.62 %
Intra-Subject CV	9.84 %	8.91 %	20.13 %

[1] Calculated using least-squares means according to the formula: $e^{(\text{Irbesartan-HCTZ (A) - Coaprovel (B)})} \times 100$
[2] 90% Geometric Confidence Interval using ln-transformed data
* For this parameter, N = 52.
** For this parameter, N = 51.

SUMMARY OF RESULTS
HYDROCHLOROTHIAZIDE
N = 53

Pharmacokinetic Parameters

Parameters		Test (Irbesartan-HCTZ (A)) Mean	SD	CV (%)	Reference (Coaprovel (B)) Mean	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	453.11	125.01	27.59	465.81	119.22	25.59
AUC_{0-inf}	(ng·h/mL)	475.78	124.83	26.24	489.36	120.76	24.68
C_{max}	(ng/mL)	72.77	23.31	32.04	76.28	22.72	29.79
Residual area	(%)	5.14	2.31	44.94	5.01	1.98	39.44
T_{max}	(h)	1.89	0.79	41.48	2.05	0.80	39.04
T_{max}*	(h)	1.67	0.67	-	2.00	0.83	-
K_{el}	(h^{-1})	0.0700	0.0110	15.64	0.0711	0.0109	15.33
$T_{½ el}$	(h)	10.14	1.62	15.93	9.96	1.43	14.31

* Medians and interquartile ranges are presented.

Irbesartan-HCTZ (A) vs Coaprovel (B)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	97.63%	97.64%	95.34%
90 % Geometric C.I.[2]	94.33 % to 101.04 %	94.66 % to 100.71 %	90.45 % to 100.48 %
Intra-Subject CV	9.98 %	8.99 %	15.31 %

[1] Calculated using least-squares means according to the formula: $e^{(\text{Irbesartan-HCTZ (A) - Coaprovel (B)})} X\ 100$

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

Protocol deviations:

There were 5 deviations reported in this study. Two deviations were related to unacceptable humidity level in medication storage, one deviation was linked to inappropriate blood sampling. Two participants failed to complete post-study procedures within requested timeframe. These deviations are considered normal and acceptable since they do not alter the validity of the study conclusion.

Safety data

The safety analysis includes the 56 subjects who entered the study and received at least one of the treatments. A total of 47 post-dose adverse events were reported by 23 subjects. 23 adverse events were reported in subjects receiving the test and 24 adverse events were reported in those receiving the reference product.

The safety profile of both products seems to be comparable although the design was not powered to compare the safety profile. No difference in the safety profile is anticipated.

Study for the 300/12.5 mg strength

Methods

Study was a single centre, single dose, randomized, open-label, 2-way crossover, bioequivalence study of irbesartan-HCT 300/12.5 mg tablet and CoAprovel (reference) following a 300/12.5 mg dose in healthy subjects under fasting conditions. Blood samples for irbesartan and HCT were each drawn into blood collection tubes containing EDTA K2 prior to drug administration and at 0.33, 0.67, 1.00, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, and 48 hours post-dose in each period. For irbesartan only additional sample was obtained 72 hours post-dose. The treatment phases were separated by a washout period of 7 days.

This study was performed by a Qualified Investigator in clinical facilities of the CRO.

The clinical study protocol (dated 07/02/2007) was approved by the Ethics Committee on 15/02/2007. Amended study protocol 1 (dated 10/04/2007) was approved by the Ethics Committee on 17/04/2007. The clinical phase was performed in two groups. Subjects of group 1 were tested between 22/03/2007 and 01/04/2007. Subjects of group 2 were dosed between 24/05/2007 and 03/06/2007
The analysis of the samples was conducted in the period from 15/06/2007 to 07/07/2007.

Test and reference products

Treatment A: irbesartan/hydrochlorothiazide 300/12.5 mg film-coated tablets. Teva Pharmaceuticals Industries Ltd., Israel. Manufacture Date: 28/01/2007.
Treatment B: CoAprovel TM (irbesartan/hydrochlorothiazide), Sanofi Winthrop Industrie, France
Expiration date: 03/2009.

Population studied

Fifty-six healthy subjects were included in the study. All 56 subjects received at least one dose of the study medication and, therefore, comprised the safety population. Fifty-two individuals who completed both treatment periods were included in the pharmacokinetic analyses. During period 1 three subjects were withdrawn due to various adverse events and one subject withdrew consent for personal reasons. In pre-dose period two subjects were withdrawn due to a positive drug screen and another two due to adverse events. These subjects were replaced. One subject was excluded from the pharmacokinetic and statistical analysis involving AUC_{0-t} due to lack of appropriate samples. As per CHMP request applicant demonstrated that bioequivalence criteria are still met after inclusion of this patient into analysis.

Analytical method

The same bioanalytical method and the same centre were employed as for the previous study.

A total of 2128 study samples of irbesartan were analyzed and 67 repeat analyses (3.15 %) corresponding to 46 study samples were performed. Six samples were reanalysed because of unacceptable internal standard response, 22 due to loss of sample during processing, 9 samples were reanalysed due to the internal standard response being lower than or equal to 5% of the mean internal standard responses, 28 samples because sample concentration being above upper limit of quantitation and 2 samples were reanalyzed to obtain confirming value.

For hydrochlorothiazide a total of 2022 study samples were analyzed and 169 repeat analyses (8.37 %) corresponding to 169 study samples were performed. Eleven samples were reanalysed because of loss of sample during processing, 1 sample was reanalysed due to the internal standard response is lower than or equal to 5% of the mean internal standard responses, 5 samples because sample concentration above upper limit of quantitation and 152 samples were repeated or re-injected by error.

The validation of the analytical method is satisfactory

Pharmacokinetic variables

Standard pharmacokinetic parameters were calculated through non-compartmental analyses of pharmacokinetic parameters and statistical analyses using Bioequiv (release 3.50), a proprietary software developed and tested for bioequivalence studies.

Statistical methods

For both irbesartan and hydrochlorothiazide, analysis of variance was performed on the ln-transformed data of AUC_{0-t}, AUC0-inf and C_{max}. ANOVA was also carried out on the untransformed data of T1/2 el and K_{el}. A conventional statistical analysis was performed with the model including sequence, subject within sequence, period and treatment as factors. The sequence effect was tested using subjects within sequence effect as the error term. The treatment and period effects were tested against the residual mean square error.
Criteria for bioequivalence for irbesartan and hydrochlorothiazide were 90% geometric CI of the ratio of least-squares in means from the ANOVA of the ln-transformed AUC_{0-t} and C_{max} should be within 80% to 125%.

Results

All pre-dose samples were found to be below the LLOQ for both drugs, except in one case with irbesartan.
For irbesartan T_{max} median was 1.00 h for test and 1.33 h for reference. For hydrochlorothiazide T_{max} was 1.67 for the test and 2.00 for the reference. The non-parametric analysis of T_{max} shows a statistical significant difference in both cases, which is considered clinically irrelevant. The non-parametric 90% CI has not been provided.
For irbesartan the minimum C_{max} value was 1455.36 ng/mL and the maximum C_{max} value was 12354.54 ng/mL. For hydrochlorothoazide the minimum C_{max} value was 44.73 ng/mL and the maximum C_{max} value was 165.94 ng/mL.
No statistically significant difference ($\alpha = 0.05$) was detected between the periods or the sequences for the primary variables of the study (C_{max}, AUC_t).

Summary of Pharmacokinetic Results

Irbesartan

N = 51

Parameters		Test (Irbesartan-HCTZ (A)) Mean	SD	CV (%)	Reference (Coaprovel (B)) Mean	SD	CV (%)
AUC_{0-t***}	(ng·h/mL)	19276.25	7855.08	40.75	20500.68	10008.88	48.82
$AUC_{0-inf**}$	(ng·h/mL)	20708.19	8265.57	39.91	22414.67	10365.58	46.24
C_{max}	(ng/mL)	3746.34	1282.69	34.24	3558.00	1749.19	49.16
Residual area**	(%)	5.85	4.91	83.90	6.87	6.55	95.25
T_{max}	(h)	1.51	1.15	76.61	1.78	1.10	61.95
T_{max}*	(h)	1.00	1.00	-	1.33	1.25	-
K_{el**}	(h^{-1})	0.0570	0.0261	45.71	0.0551	0.0242	43.81
$T_{½ el**}$	(h)	14.36	5.76	40.10	16.31	10.39	63.69

* Medians and interquartile ranges are presented.
**For these parameters, N = 49.
***For this parameter, N = 50.

Irbesartan-HCTZ (A) vs Coaprovel (B)

	AUC_{0-t**}	AUC_{0-inf*}	C_{max}
Ratio[1]	94.44%	93.14%	107.75%
90 % Geometric C.I.[2]	87.51 % to 101.93 %	86.30 % to 100.52 %	98.37 % to 118.03 %
Intra-Subject CV	22.23 %	21.98 %	27.30 %

[1] Calculated using least-squares means according to the formula: $e^{(\text{Irbesartan-HCTZ (A) - Coaprovel (B)})} \times 100$
[2] 90% Geometric Confidence Interval using ln-transformed data
* For this parameter, N = 49.
** For this parameter, N = 50.

Summary of Pharmacokinetic Results

Hydrochlorothiazide

N = 52

Parameters		Test (Irbesartan-Hydrochlorothiazide (A)) Mean	SD	CV (%)	Reference (Coaprovel (B)) Mean	SD	CV (%)
AUC_{0-t}**	(ng·h/mL)	532.93	132.99	24.95	529.18	174.77	33.03
AUC_{0-inf}**	(ng·h/mL)	554.24	132.38	23.89	550.82	172.58	31.33
Residual area**	(%)	4.05	1.58	38.91	4.34	2.20	50.77
C_{max}	(ng/mL)	90.51	27.77	30.69	86.79	28.89	33.29
T_{max}	(h)	1.79	0.72	40.15	2.22	0.92	41.60
T_{max}*	(h)	1.67	0.67	-	2.00	0.83	-
K_{el}**	(h^{-1})	0.0756	0.0108	14.26	0.0764	0.0125	16.39
$T_{½ el}$**	(h)	9.35	1.35	14.41	9.32	1.61	17.24

*Medians and interquartile ranges are also presented.

**For these parameters, N = 51.

Irbesartan-HCTZ (A) vs Coaprovel (B)

	AUC_{0-t}*	AUC_{0-inf}*	C_{max}
Ratio[1]	102.19%	101.94%	104.93%
90 % Geometric C.I.[2]	97.70 % to 106.89 %	97.78 % to 106.28 %	99.12 % to 111.08 %
Intra-Subject CV	13.29 %	12.32 %	17.18 %

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

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

*For these parameters, N = 51.

Protocol deviations

There were 8 deviations reported in this study. Three deviations were related to unacceptable humidity level in medication storage, four deviations were linked to consumption of prohibited food by study participants. One participant failed to complete post-study procedures. These deviations are considered normal and acceptable since they do not alter the validity of the study conclusion.

Safety data

The safety analysis includes the 56 subjects who entered the study and received at least one of the treatments. A total of 116 post-dose adverse events were reported by 41 subjects. 45 adverse events were reported in subjects receiving the test and 71 adverse events were reported in those receiving the reference product.

The safety profile of both products seems to be comparable although the design was not powered to compare the safety profile. No difference in the safety profile is anticipated.

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 excipents is similar,
- the dissolution profile should be similar under identical conditions for the additional strength and strength of the batch used in bioequivalence study.

Bullet point 1 is justified by a Declaration of the Manufacturer: "The 150/12.5 mg and 300/25 mg strengths of Irbesartan/Hydrochlorothiazide Film-Coated Tablets are produced by the same manufacturer, Teva Pharmaceutical Industries Ltd., Kfar Saba, Israel. Both strengths are manufactured using the same manufacturing process applying well-established wet granulation technology".
With regard to bullet point 2 the literature data on irbesartan and hydrochlorothiazide confirm that the pharmacokinetics of both compounds is linear:
- The innovator, CoAprovel, Summary of Product Characteristics states "Irbesartan exhibits linear and dose proportional pharmacokinetics over the dose range of 10 to 600 mg".
- According to the article "Pharmacokinetics of Hydrochlorothiazide in Man" (B. Beermann and Margaretha Groschinsky-Grind European Journal of Clinical Pharmacology 12, 297-303 (1977), included in Annex IV), the gastrointestinal absorption of hydrochlorothiazide is linear in the dose range of 5-75 mg
Bullet points 3 and 4 are fulfilled taking in account the composition of the core of the tablets.
Bullet point 5 is addressed by comparative dissolution profiles that demonstrate similar dissolution profiles of Irbesartan/Hydrochlorothiazide 150/12.5 mg and 300/25 mg, which by initial CHMP assessment was not sufficiently demonstrated. After repeated assessment it was concluded that dissolution profiles are not similar, but the difference is similar to that observed in the reference product and, therefore, it is acceptable.

Conclusions

Based on the presented bioequivalence studies Irbesartan/Hydrochlorothiazide Teva is considered bioequivalent with CoAprovel.

The results of the study with the 150/12,5 mg formulation can be extrapolated to the 300/25 mg strength, 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 company must ensure that this system is in place and functioning before the product is placed on the market.

- **Risk Management Plan**

The application is based on a reference medicinal product for which no safety concerns requiring specific risk minimization activities have been identified.

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 that the benefit/risk ratio of Irbesartan/Hydrochlorothiazide Teva in the treatment of hypertension was favourable and therefore recommended the granting of the marketing authorisation.