EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 February 2012
EMA/225623/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sabervel

International non-proprietary name: **irbesartan**

Procedure No. **EMEA/H/C/002510**

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

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Table of contents

Background information on the procedure

1.1. Submission of the dossier

The applicant Pharmathen S.A. submitted on 5 May 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Sabervel, through the centralised procedure under Article 3(3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 February 2011.

At the time of submission the proposed name for this medicinal product was Irbesartan Pharmathen. The name was changed to Sabervel during the procedure (day 121).

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication: treatment of essential hypertension and treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive drug regimen.

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

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

Information on paediatric requirements

Not applicable

The chosen reference product is:

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

- Product name, strength, pharmaceutical form: Aprovel 75mg, 150 mg and 300mg
- Marketing authorisation holder: Sanofi Pharma Bristol Myers Squib SNC
- Date of authorisation: 27-08-1997
- Marketing authorisation granted by:
  - Community
    - Community Marketing authorisation number: EU/1/97/046/001-039

■ Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Aprovel 75mg, 150 mg and 300mg
- Marketing authorisation holder: Sanofi Pharma Bristol Myers Squib SNC
- Date of authorisation: 27-08-1997
- 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 300 mg film-coated tablets
- Marketing authorisation holder: Sanofi Pharma Bristol Myers Squib SNC
- Date of authorisation: 27-08-1997

- Marketing authorisation granted by:
  - Community Marketing authorisation number(s): EU/1/97/046/026-030
    EU/1/97/046/033
    EU/1/97/046/036
    EU/1/97/046/039
- Bioavailability study number(s): 2006-004029-27

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 Rapporteur appointed by the CHMP and the evaluation team was:

Rapporteur: Concepcion Prieto Yerro

- The application was received by the EMA on 5 May 2011.
- The procedure started on 25 May 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 August 2011.
- During the meeting on 19-22 September, 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 September.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 November 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 31 December 2011.
- During the CHMP meeting on 16-19 January, 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 25 January 2012.
- During the meeting on 13-16 February, 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 Sabervel on 16/02/2012.

2. Scientific discussion

2.1. Introduction

Sabervel 75 mg, 150 mg and 300 mg film-coated tablets is a generic medicinal product containing irbesartan as active substance. The reference medicinal product is Aprovel 75 mg, 150 mg and 300 mg film-coated tablets from Sanofi Pharma Bristol-Myers Squibb SNC, which was centrally authorized on 27 August December 1997. The active substance of the reference product is irbesartan.

Irbesartan is a nonpeptide tetrazole derivative, which is a potent, orally active, selective angiotensin II receptor (type AT1) antagonist. 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.

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 Sabervel is the same as authorised for the reference medicinal product Aprovel. Irbesartan is indicated in adults for the treatment of essential hypertension. It is also indicated for the treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive medicinal product regimen.

2.2. Quality aspects

2.2.1. Introduction

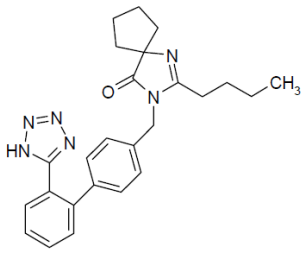
Sabervel is presented as film-coated tablets containing irbesartan as active substance. Three strengths have been developed: 75 mg, 150 mg or 300 mg. Excipients used in the preparation of Sabervel are well known excipients used in tablet preparations such as lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, silica colloidal anhydrous, hypromellose, magnesium stearate (present in the tablet core), and Opadry Y-1-7000 white (coating agent) which is composed of hypromellose, titanium dioxide (E171), and macrogol 4000.

Sabervel is presented as white, concave, round film-coated tablets. The diameter of the tablets varies depending on the strength (75mg- 7 mm diameter, 150 mg – 9 mm diameter, 300 mg-11 mm diameter).

The tablets are packed in white PVC/PVDC/alu-PVDC blisters.

2.2.2. Active substance

The active substance is irbesartan, a well known active substance described in Ph.Eur. It is chemically designated as 2-Butyl-3-[p-(O-1*H*-tetrazol-5-yl-phenyl)benzyl]-1,3-diazaspiro-[4.4]non-1-en-4-one or 2-Butyl-3[(2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl]-1,3-diazaspiro-[4.4]non-1-en-4-one and has the following structure:



Irbesartan is a white to off-white crystalline, non hygroscopic powder, which is slightly soluble in ethanol (96%), chloroform and methylene chloride, and practically insoluble in water. Irbesartan is practically insoluble at acidic pHs. Its solubility increases when increasing the pH, becoming slightly soluble around pH 9 and freely soluble at around pH 13.

Irbesartan has no chiral centers and exhibits no stereoisomerism. The chemical structure of the molecule has been established by spectral (UV, IR, ^{1}H and ^{13}C NMR and mass spectra) and elemental analyses.

Two crystalline polymorph forms of irbesartan are known from the literature: form A and form B. X-ray powder diffraction, DSC and IR analysis confirmed that the manufacturing processes used consistently produce polymorphic form A. In addition stability data showed that irbesartan form A is a highly stable crystalline form, and it does not convert to the other crystalline form in any of the conditions tested.

Manufacture

Irbesartan is supplied by different manufacturers, and an Active Substance Master Files (ASMF) has been submitted for each manufacturer. The manufacturing processes of irbesartan have been adequately described and satisfactory specifications have been set for starting materials, reagents, solvents and auxiliary materials used. Suitable in-process controls to ensure quality of the final compound have been established.

Irbesartan active substance is packaged into a polyethylene or an aluminum laminate bag. This bag is further introduced into a second aluminum foil bag again, which is sealed and placed in a fibrous drum. Specifications and analytical reports for the packaging components have been presented and the suitability of the polyethylene bags for use with food and pharmaceuticals has been confirmed.

Specification

The specification of irbesartan was set to be in line with the current Ph.Eur. monograph and relevant ICH guidelines. It includes tests for appearance, solubility, identification (FTIR, HPLC and XRD), water content (Ph. Eur.), heavy metals (Ph.Eur.), sulphated ash (Ph.Eur.), appearance of solution (Ph. Eur.), related substances (HPLC), residual solvents (GC) and assay (Ph.Eur.).

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

The residual solvents are also controlled at release with specifications in accordance with ICH Q3C (R3).

The specification proposed is considered suitable to control the quality of the drug substance manufactured using the current processes.

Non-compendial analytical procedures have been satisfactorily described and validated in accordance with the ICH Q2 (R1) guideline. The 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 processes in the proposed manufacturing sites has been provided. All batches represented full scale production and complied with the requirements in the drug substance specification. These results confirm batch-to-batch consistency and compliance with the proposed specification.

Stability

Data from stability studies on three production scale batches have been provided. Samples were stored for up to 36 or 48 months under long term conditions (25°C/60% RH) and for 6 months under accelerated conditions (40°C/75% RH) in accordance with ICH requirements. All batches have been tested for conformance with the specifications using stability indicating analytical methods. In all cases the batch analysis data met the predefined specifications and no significant changes were observed.

In addition stability data have been provided under stress conditions (heat, acid hydrolysis, base hydrolysis, photo degradation, water hydrolysis and hydrogen peroxide treatment). The proposed retest period of three years for the drug substance, stored in the proposed packaging material, is supported by the stability results provided.

2.2.3. Finished medicinal product

Pharmaceutical development

The aim of the pharmaceutical development was to obtain immediate-release tablets containing qualitatively and quantitatively the same active substance, and exhibiting comparable dissolution profiles and the same bioavailability as the reference medicinal product, Aprovel.

Sabervel film-coated tablets contain lactose monohydrate, cellulose microcrystalline, croscarmellose sodium, silica colloidal anhydrous, hypromellose and magnesium stearate. The formulation of Sabervel does not contain pregelatinised maize starch or poloxamer 188, as the reference medicinal product does. All the excipients employed are widely used in the production of tablets and comply with the Ph. Eur.

The development approach was to obtain a unique granulate to tablet proportionally at different weight for each dose. Hence, the 75 mg tablet has a final weight of 125 mg, the 150 mg tablet a weight of 250 mg and the 300 mg tablet a weight of 500 mg.

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

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

Since Irbesartan film-coated tablets application concerns several strengths (300 mg, 150 mg and 75 mg) of active substance and the condition of dose proportionality is complied according to CPMP/EWP/QWP/1401/98 rev1, only one bioequivalence study of one strength (300 mg) has been carried out.

Adventitious agents

None of the excipients used in the drug product is of human or animal origin, with the exception of lactose monohydrate. Lactose monohydrate is derived from milk and calf rennet and is therefore compliant with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and Veterinary Medicinal Products (EMEA/410/01 Rev. 3).

Magnesium stearate used in the formulation is of vegetal origin.

Manufacture of the product

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

A flow diagram and detailed description of the manufacturing process have been provided. The process has been sufficiently described. Several in-process controls have been identified.

Irbesartan shows polymorphism. Adequate data has been presented to confirm that the polymorphic form of the active substance does not change during the manufacturing process or during the storage of the medicinal product.

A validation protocol has been provided and the applicant has committed to conduct the manufacturing process validation on three consecutive industrial batches of Irbesartan 300 mg film-coated tablets, Irbesartan 150 mg film-coated tablets and Irbesartan 75 mg film-coated tablets according with the CPMP guideline QWP/848/96 on process validation.

Product specification

The product specification is a standard one for tablets and contains tests with suitable limits for appearance, uniformity of mass (Ph. Eur), hardness (Ph. Eur.), water content (Ph. Eur.), uniformity of dosage units by mass variation (Ph. Eur.), dissolution (Ph. Eur.), identification by HPLC and TLC (Ph. Eur.), assay (Ph. Eur.), related substances (Ph. Eur.), and microbial contamination (Ph. Eur.). The specification and control test applied for the finished product is considered appropriate for this dosage form, and it is in compliance with Ph. Eur. and ICH Q6A guideline.

All the analytical methods have been satisfactorily described. All non pharmacopoeial methods have been satisfactory validated in accordance with the ICH Q2 (R1).

Batch analysis data for each strength have been provided on five pilot scale batches of the finished product (2 or 3 batches manufactured with active substance from a different supplier). Batch analysis results confirm that the film-coated tablets can be manufactured reproducibly according to the finished product specification.

Stability of the product

Stability studies under ICH conditions of 25ºC/60%RH (long term, 48 months) and 40ºC/75%RH (accelerated, 6 months) were carried out on five pilot scale batches of Sabervel 75 mg or 300 mg film-coated tablets manufactured with active substance sourced from the two active substance manufacturers (two batches from one and three from the other). All of them have the same formulation and are packaged in the same container closure system proposed for marketing.

Sabervel 150mg film-coated tablets were not placed on stability study as according to ICH Q1D, the stability of the intermediate dose is represented by the stability of the extremes tested.

All batches were tested for physical and technological (appearance, dissolution), chemical (assay, degradation products) and microbiological parameters using stability indicating methods. In all cases the parameters tested remained within the proposed specifications and no significant changes were observed.

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

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

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture, packaging and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC.

2.3. Non- clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Environmental Risk Assessment

No Environmental Risk Assessment (ERA) was submitted. This was justified by the Applicant as the introduction of Sabervel is considered unlikely to result in any significant increase in the combined sales volumes for all irbesartan containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for Sabervel film-coated tablets containing irbesartan. To support the marketing authorisation application the Applicant conducted one bioequivalence study with cross-over design after a single dose under fasting conditions. This study was the pivotal study for the assessment.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of irbesartan based on published literature. The SmPC is in line with the SmPC of the reference product.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

GCP

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

2.4.2. Pharmacokinetics

Methods and study design

Study GE03IRB/1/06

This study was a single-dose, randomized, open-label, two-way crossover, comparative bioavailability study of Irbesartan 300 mg tablets (J. Uriach y Compañía, S.A.) and Aprovel 300 mg film-coated tablets (Sanofi Pharma Bristol-Myers Squibb SNC, Spain) in normal, healthy subjects under fasting conditions.

The washout period was a minimum of 7 days between each dosing, but no more than 14 days. The wash-out was considered adequate since the drug has a long half-life (11-15 hours) and pre-dose levels were not detected. Moreover, 5% levels of the lowest Cmax for irbesartan (68.59 ng/mL) could be detected with this LLOQ (25.08 ng/mL).

Test and reference products

Test Product: Irbesartan 300 mg film coated tablets, manufactured by J. Uriach y Compañía, S.A., Spain. Batch number: Z002 (biobatch: 0701). Batch size: 100,000 film coated tablets. Assay (content): 98.89% of label claim.

Reference Product: Aprovel 300 mg film coated tablets, manufactured by Sanofi Pharma Bristol-Myers Squibb SNC (marketed in Spain). Batch number: 2525 (biobatch 0701). Assay (content): 97.04% of label claim.

Mode of Administration

The subjects included in the study were divided in 5 groups and all performed two experimental sessions, leaving a washout period of 7 days.

The subjects were assigned to one of two treatment sequences Test/Reference (TR) and Reference/Test (RT) using a SPSS v14.0 program, in a balanced way (an equal number of subjects in each treatment sequence). Subjects were randomised in 4 blocks of 7 subjects.

Population studied

A total of 47 young subjects were initially selected; 29 were included in the study (14 male and 15 female) and 28 were analysed.

The basic demographic data such as sex, age, weight and height of all 29 subjects enrolled into the study are presented in the table below.

Parameter	Mean (s.d.)	(min-max)	Units
Age	25.21 (4.20)	(19.00-35.00)	years
Body weight	67.50 (10.97)	(51.00-84.50)	Kg
Height	171.31 (9.83)	(150.00-188.00)	cm
Quetelet's index	22.85 (1.68)	(19.50-25.40)	Kg/m^2

Analytical methods

The pre-study validation of the analytical method was satisfactory. No (outlier) value was excluded from calculations.

The in-study validation shows acceptable calibration standards (zero) and QC values.

The LLOQ (20.08 ng/mL) was lower than 5% of the minimum Cmax. Therefore, in case a carry-over effect was present it would have been detected.

The long-term stability data in frozen human plasma cover the period of time that the samples have been stored in this study.

Pharmacokinetic variables

The main standard pharmacokinetic variables (AUC_{0-t}, $AUC_{0-\infty}$, C_{max}) were determined through non-compartmental analysis by the linear log trapezoidal rule.

As other secondary pharmacokinetic variables t_{max}, K_{el}, $t_{1/2}$ and % extrapolated area were assessed.

Statistical methods

The comparative study of the bioequivalence parameters Ln (AUC_{0-t}), Ln ($AUC_{0-\infty}$) and Ln C_{max} was performed by means of ANOVA, controlling for the sequence, subjects nested in the sequence, the period and the formulation; in order to obtain an estimation of the residual variance and determine the role of these factors.

Bioequivalence was concluded if the 90% IC of the relative mean AUC y C_{max} were included within 80-125% limits according EMA guidance. T_{max} was analyzed by the non-parametric Hauschke method.

The pharmacokinetic analysis based on the linear trapezoidal rule is considered adequate.

The statistical analysis performed is parametric, except for Tmax, in accordance with the Guideline on the investigation on bioequivalence.

Results

Figure 1: Mean of plasma concentration/time linear curves following 300 mg single oral dose

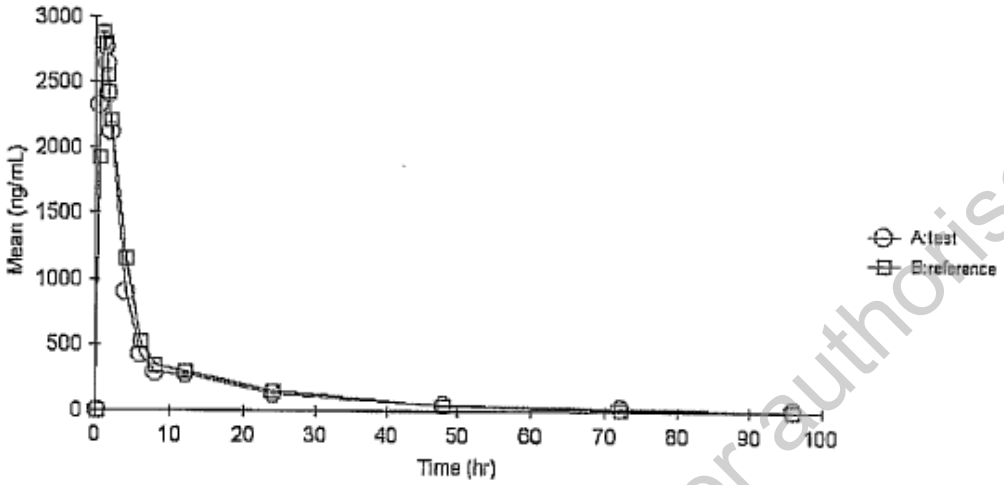
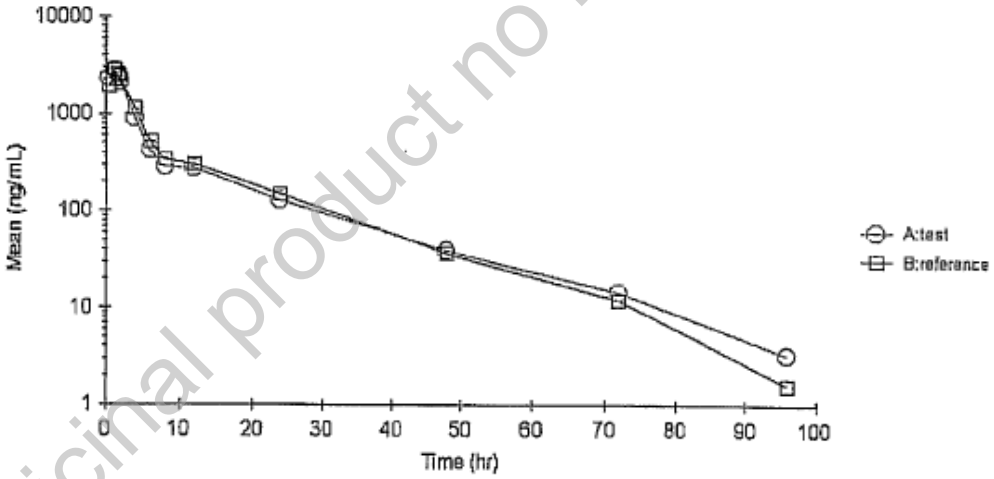


Figure 2. Mean of plasma concentration/time log-linear curves following 300 mg single oral dose



Pharmacokinetics parameters of Irbesartan for both formulations

Parameters	Test formulation (Irbesartan) Arithmetic mean (s.d.) Median [minimum- maximum]	Reference formulation (Aprovel®) Arithmetic mean (s.d.) Median [minimum- maximum]
AUC_0^t (ng•h /L)	15332.49 (6161.55) 15414.57[6794.67-36092.51]	16345.55 (6812.17) 15464.86 [4785.55-37063.74]
AUC_0^∞ (ng•h/L)	16394.00 (6227.54) 16099.90 [7365.65-37392.50]	17266.42 (6747.54) 16317.86[5924.93-37837.12]
C_{max} (ng/L)	3345.17 (1134.50) 3087.43[1371.87-6265.08]	3240.35 (1225.76) 2940.14[1596.77-6845.76]
t_{max} (h)	1.36 (0.86) 1.13[0.50-4.0]	1.44 (1.00) 1.13[0.50-4.0]
$t_{1/2}$ (h)	16.47 (10.17) 14.42 [2.18-40.17]	14.60 (8.19) 13.0 [2.83-34.97]
λz (1/h)	0.07 (0.06) 0.05 [0.02-0.032]	0.07 (0.05) 0.05 [0.02-0.24]
% AUC extrapolated	7.01 (4.92) 6.51 [1.19-20.38]	6.30 (4.24) 5.30 [1.37-19.23]
Vz/F (L)	460.25 (277.62) 401.60 [101.57-1108.48]	401.27 (265.31) 347.25 [121.37-1210.32]
Cl/F(L/h)	20.80 (7.8) 18.63 [8.02-40.73]	20.20 (8.79) 18.41 [7.93-50.63]

Bioequivalence assessment

Parameter	Transf.	T/R Ratio (%)	Pr > |t|	Alpha	Lower CL	Upper CL	Equivalence Limits (%)
AUC 0-inf	Log	95.767	0.2537	0.1	88.902	102.015	80 – 125
AUC 0-t	Log	94.997	0.2137	0.1	88.691	101.751	80 – 125
Cmax	Log	103.819	0.3860	0.1	96.558	111.627	80 – 125

Based on the statistical analysis submitted by the Applicant both 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).

Absence of quantifiable levels in pre-dose samples indicates a lack of carryover effect. Therefore, an unequal carry-over effect can be excluded and the cross-over design can be considered to represent the relative bioavailability between test and reference products.

The AUC estimated is considered representative enough of the extent of absorption/exposure since the extrapolation is lower than 20% in all but one of the individual profiles.

The LLOQ was 20.08 ng/mL, therefore, it was considered sensitive enough to detect levels of 5% of the minim Cmax (68.59 ng/mL) to exclude the possibility of a relevant carry-over effect.

The non-parametric 90% CI of Tmax has not been provided, which is considered acceptable since Tmax is not critical for onset of action.

Safety data

No serious AEs were reported during the conduct of this study. There were Fifteen (15) adverse events. Eight (8) AEs were reported in subjects under reference treatment and seven (7) AEs when they were under test treatment. Only five (5) AEs were related with study drug in both groups of treatment. The main AEs were migraine (7 cases) and sickness (4 cases).

Conclusions

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

The results of study GE03IRB/1/06 with the 300 mg formulation can be extrapolated to the other strengths 75mg and 150 mg, according to conditions in the Guidelines.

Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

Safety

The safety profile of Sabervel seems to be comparable with Aprovel although it is obvious that the design of the PK study undertaken was not powered to compare the safety profile. No difference in the safety profile can be anticipated.

2.4.3. Post marketing experience

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

2.4.4. Conclusions on clinical aspects

Bioequivalence between the test product and the reference product has been shown in a cross-over study after a single dose in fasting conditions.

A waiver of two proportional strengths has been applied for based on dissolution profiles. The different tablet strengths are manufactured with the same process, they have the same qualitative composition and a proportional quantitative composition in the tablet core and the dissolution profiles have been shown to be sufficiently similar. Therefore, a biowaiver can be granted and the bioequivalence shown for the 300 mg strength can be extrapolated to the proportional strengths of 75 and 150 mg.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

The MAH must ensure that the system of pharmacovigilance, as 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 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 require additional risk minimisation activities, this approach is considered acceptable.

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

PSUR submission

The PSUR submission schedule should follow the PSUR schedule for the reference product, which currently is on a 3-yearly cycle. The next data lock point for the reference medicinal product is 11 August 2012.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a generic version of irbesartan film-coated tablet. The reference product Aprovel is indicated for 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. No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a cross-over design after a single dose under fasting conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements.

Irbesartan exhibits linear and dose proportional pharmacokinetics over the dose range of 10 to 600 mg. As indicated in the Guideline on investigation of bioequivalence "evaluation of bioequivalence should be based upon measured concentrations of the parent compound". Therefore, there was no need to measure any other analyte different to the parent compound.

The use of the highest dose and strength in case of linear kinetics is recommended for analytical reasons and solubility reasons except in case of safety concerns.

Irbesartan's absorption is independent of food intake, therefore a 2x2 cross-over single dose study in fasting conditions is considered adequate to compare two formulations containing the same drug, when the drug can be taken with or without food and the formulations is a conventional formulation. Consequently, a single dose study in fasted state was considered the most adequate study design to investigate the pharmacokinetic bioequivalence of irbesartan.

Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Sabervel met the protocol-defined criteria for bioequivalence when compared with Aprovel. The point estimates and their 90% confidence intervals, and Cmax were all contained intervals for the parameters AUC0-t,, AUC0- within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

A waiver of two proportional strengths has been applied for based on dissolution profiles. The different tablet strengths are manufactured with the same process, they have the same qualitative composition and a proportional quantitative composition in the tablet core and the dissolution profiles have been

shown to be sufficiently similar. Therefore, a waiver can be granted and the bioequivalence shown for the 300 mg strength can be extrapolated to the proportional strengths of 75 and 150 mg.

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.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Irbesartan Pharmathen 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 is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

Pharmacovigilance System

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

Risk management system

Not applicable.

PSUR cycle

The PSUR cycle for the product will follow PSURs submission schedule for the reference medicinal product.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable