16 December 2010
EMA/99460/2011
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Ifirmacombi

International nonproprietary name: Irbesartan / Hydrochlorothiazide

Procedure No. EMEA/H/C/002302

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 7418 8545
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Table of contents

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Krka, d.d., Novo mesto submitted on 6 May 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Ifirmacombi, through the centralised procedure falling within the scope of the Article 3 (3) – 'Generic of a Centrally authorised product' of Regulation (EC) No. 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 April 2008.

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

The application concerns a generic medicinal product as defined in Article 10(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 European Union on the basis of a complete dossier in accordance with Article 6 of Directive 2001/83/EC.

The applicant applied for the following indication:

Treatment of essential hypertension.
This fixed dose combination is indicated in adult patients whose blood pressure is not adequately controlled on irbesartan or hydrochlorothiazide alone

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: CoAprovel, 300 mg/25 mg, 300 mg/12.5 mg, 150 mg/12.5 mg film-coated tablet
- Marketing authorisation holder: Sanofi Pharma Bristol-Myers Squibb SNC
- Date of authorisation: 15-10-1998
- Marketing authorisation granted by:
  - Community
    - Community Marketing authorisation number: EU/1/98/086/011 - 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, pharmaceutical form: CoAprovel, 300 mg/25 mg, 300 mg/12.5 mg film-coated tablet
- Marketing authorisation holder: Sanofi Pharma Bristol-Myers Squibb SNC
- Date of authorisation: 15-10-1998
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number(s): EU/1/98/086/016 – 020, EU/1/98/086/022 – 028, EU/1/98/086/030 - 031, EU/1/98/086/033 - 034

The Rapporteur appointed by the CHMP was Concepcion Prieto Yerro.

Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

Licensing status:

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

1.2. Steps taken for the assessment of the product

- The application was received by the Agency on 6 May 2010.
- The procedure started on 26 May 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 August 2010.
- During the meeting on 20-23 September 2010, 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 24 September 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 15 October 2010.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 26 November 2010.
- During the meeting on 13-16 December 2010, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Ifirmacombi on 16 December 2010.

2. Scientific discussion

2.1. Introduction

Ifirmacombi film-coated tablets is a generic medicinal product containing the active substances Irbesartan (as hydrochloride) and Hydrochlorothiazide. The reference medicinal product is CoAprovel 300 mg/25 mg, 300 mg/12.5 mg and 150 mg/12.5 mg film-coated tablets, containing Irbesartan in the form of free base. CoAprovel was authorised on 15 October 1998. Both medicinal products are administered orally. Bioequivalence has been demonstrated to the reference medicinal product.

Irbesartan is a potent, selective angiotensin-II receptor (AT1 subtype) antagonist active through oral administration. 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 in patients without risk of electrolyte imbalance. 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.

Hydrochlorothiazide is a thiazide diuretic. The mechanism of antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity, increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. Presumably through blockade of the renin-angiotensin-aldosterone system, co-administration of irbesartan tends to reverse the potassium loss associated with these diuretics. With hydrochlorothiazide, onset of diuresis occurs in 2 hours, and peak effect occurs at about 4 hours, while the action persists for approximately 6-12 hours.

The combination of hydrochlorothiazide and irbesartan produces dose-related additive reductions in blood pressure across their therapeutic dose ranges. The addition of 12.5 mg hydrochlorothiazide to 300 mg irbesartan once daily in patients not adequately controlled on 300 mg irbesartan alone resulted in further placebo-corrected diastolic blood pressure reductions at trough (24 hours post-dosing) of 6.1 mm Hg. The combination of 300 mg irbesartan and 12.5 mg hydrochlorothiazide resulted in overall placebo-subtracted systolic/diastolic reduction of up to 13.6/11.5 mm Hg.

The safety and efficacy profile of irbesartan and hydrochlorothiazide has been demonstrated in several clinical trials, details of which can be found in the EPAR of the reference product CoAprovel. In addition, there is long-term post-marketing experience contributing to the knowledge of the clinical use of this product. Since this application is a generic application referring to the reference medicinal product CoAprovel, a summary of the clinical data of irbesartan free base and hydrochlorothiazide has been provided and no new clinical studies regarding pharmacology, pharmacokinetics and efficacy and safety have been conducted with irbesartan hydrochloride/hydrochlorothiazide.

The indication proposed for Ifirmacombi is the same as the authorised indication for the reference medicinal product:

"Treatment of essential hypertension.

This fixed dose combination is indicated in adult patients whose blood pressure is not adequately controlled on irbesartan or hydrochlorothiazide alone."

2.2. Quality aspects

2.2.1. Introduction

Ifirmacombi is presented in the form of biconvex film-coated tablets which differ in shape and colour depending on strength. 150/12.5 mg film-coated tablets are pale pink and oval, 300/12.5 mg strength is white, capsule shaped, and 300/25 mg film-coated tablets are of pale pink colour and capsule shape.

The film-coated tablets are composed of a combination of two active substances, irbesartan hydrochloride and hydrochlorothiazide, and excipients (defined in the SmPC section 6.1). The strength with respect to irbesartan is expressed on the free irbesartan base.

The finished product is packaged in OPA/Al/PVC//Al blisters.

2.2.2. Active Substance Irbesartan Hydrochloride

The first active substance in the combination product is Irbesartan, as hydrocholoride hydrated salt, chemical name 2-Butyl-3-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one hydrochloride sesquihydrate.

Irbesartan hydrochloride is a crystalline, white to almost white powder and is non-hygroscopic. It is sparingly soluble in ethanol, practically insoluble in chloroform and water. The substance shows polymorphism, however, the defined manufacturing process produces consistently the same crystalline form with characteristic X-ray powder diffraction pattern and characteristic IR spectrum.

Manufacture

The substance is manufactured at either of two manufacturing sites by a three-step synthesis and final purification step. The quality of the active substance is well controlled with the respect to impurity profile and residual solvents.

The manufacturing process is well described, including several critical steps. The in-process controls at the critical steps are adequate to control the reaction progress. Starting materials are defined by suitable specifications, using appropriate analytical methods. Reprocessing procedure is also sufficiently described. No intermediates are isolated.

The chemical structure of irbesartan hydrochloride has been confirmed using analytical data by 1H NMR, 13C NMR, MS, FT-IR and elemental analysis (for elements C, H, N). Melting point and XRD diffraction pattern to detect the correct polymorphic form have been also defined. All data are consistent with the proposed structure. Comparative X-ray diffraction patterns for irbesartan hydrochloride after manufacture and after 9 months at 40ºC/75% RH show that the crystalline form is not changed even during accelerated storage conditions.

Specification

As there is no monograph for irbesartan hydrochloride in Ph.Eur. (only for irbesartan free base anhydrous), the applicant developed their own specifications and test methods for the quality control. Control tests include visual appearance, solubility, identity by IR, a Ph.Eur. test for chlorides, assay

and impurities by HPLC, residual solvents by GC, water, heavy metals and sulphated ash. Particle size is not routinely tested as it shows no significant influence on dissolution rate of the finished product.

The acceptance criteria for impurities, including limits for organic impurities, inorganic impurities and residual solvents, are defined. The impurity profiles for active substance were studied and characterized in detail. Only impurities that have been found above the reporting threshold are individually monitored by the active substance specifications. The purity results of all starting materials, reagents and by-products, including potential genotoxic impurities, show that they are not carried over to the final active substance.

The limits set for specification parameters are acceptable and in line with batch results, stability studies and CHMP/ICH guidelines. Analytical methods used are sufficiently described and fully validated in line with the CHMP/ICH requirements.

Results of analysis of eight batches of the active substance were provided. Compliance with the specification was demonstrated.

Stability

Stability studies are performed in accordance with the relevant CHMP/ICH guidelines. Stability data of three production batches of the active substance up to 36 months of storage at 25°C/60% RH and 6 months at 40°C/75% RH were provided. Compliance with the specification has been confirmed at both conditions.

Irbesartan hydrochloride is unstable in basic solutions. Only slight degradation occurs in acidic and oxidizing conditions. The substance is photostable.

A suitably validated re-test period is approved, supported by the available stability data. Additional storage precautions are not needed. In accordance with EU GMP guidelines[1], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.3. Active Substance Hydrochlorothiazide

The second active substance in the finished product is hydrochlorothiazide, chemical name 6-Chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide. It is a white or almost white, almost odorless crystalline powder, very slightly soluble in water, sparingly soluble in ethanol and methanol, soluble in acetone, freely soluble in N,N-dmethylformamide, in n-butylamine and in diluted solutions of alkali hydroxides. It is practically insoluble in ether, in chloroform and in diluted mineral acids. Hydrochlorothiazide is an achiral substance. It shows polymorphism. Data confirming that the suitable polymorphic form is manufactured and then maintained during stability was provided by all manufacturers.

Manufacture

Hydrochlorothiazide from three different manufacturers is used for the finished product. In order to guarantee its quality, a valid Certificate of suitability of the European Pharmacopeia monograph (CEP) has been submitted by each manufacturer. Instead of full information on the active substance, reference is made to these CEPs.

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

Specification

The hydrochlorothiazide specifications correspond to the Ph.Eur. monograph, as confirmed also by the three CEPs provided. Certificates of analysis for three batches per active substance manufacturer were provided. All results comply with the specifications and show sufficient batch consistency.

Stability

The CEP of each active substance manufacturer includes a suitably validated re-test period in a defined container closure system, supported by the available stability data.

2.2.4. Medicinal Product

Pharmaceutical Development

The aim of the development work was to develop an immediate-release tablet equivalent to the originator's product (CoAprovel) and exhibiting the same bioavailability.

Different compositions of irbesartan/hydrochlorothiazide formulations were prepared during extensive formulation studies. The development was focused mainly on choosing the most suitable excipients to reach optimal dissolution profile.

The chosen excipients and their function are as follows: mannitol (diluent), sodium starch glycolate (disintegrant), low-substituted hydroxypropyl cellulose (binder/disintegrant), talc (glidant), hydroxypropylcellulose (binder), macrogol 6000 and hydrogenated castor oil (lubricant). For film coating, ready-to–make film coating agent Opadry II is used in pink and white colour.

All components of the finished product are well known and are routinely used in manufacture of solid oral dosage forms. Except both coating mixtures, for which an in-house specification was provided, all excipients meet pharmacopoeial requirements.

Impact of particle size of irbesartan hydrochloride and hydrochlorothiazide on dissolution has been analyzed and has no influence on performance, technological process and dissolution characteristics. Different hardness of tablets has no significant impact on dissolution rate of irbesartan and hydrochlorothiazide from irbesartan/hydrochlorothiazide film coated tablets.

No excipients of human or animal origin were used in manufacturing of Ifirmacombi film-coated tablets.

Manufacture of the Product

Wet granulation was chosen due to technological benefits which resulted in the final product meeting analytical specifications. The manufacturing process can be divided in the following steps: mixing, granulating, drying/sieving, mixing of final mixture, tabletting, coating and packaging. Adequate in-process controls and control of intermediates were established. The manufacturing process is considered a standard process according to the process validation guideline. As demonstrated by validation studies on pilot batches, the process is reproducible and capable to consistently yield product within quality specification.

Product Specification

The specification for all strengths of the finished product includes standard testing parameters typical for this kind of dosage form. The finished product is tested for identification, appearance, assay, related substances, uniformity of dosage units by content uniformity, dissolution, identification of colorants and microbiological purity. Average weight parameter was added to facilitate identification of individual strengths. The tests are performed for both active substances, as relevant. Impurities/degradation products have been evaluated and found to be acceptable from the safety perspective. The proposed test procedures and acceptance criteria follow the principles of CPMP/ICH/367/96 guideline.

Generally the same specification and limits are applied for both release and shelf-life, with identification, colorants and uniformity of dosage units tested only at release. The choice of tests and the limits are acceptable and justified.

Initial comparative dissolution profiles were provided for 300/25 mg and 150/12.5 mg strengths, which were not considered sufficient to grant a biowaiver for the 150/12.5 mg strength. Dissolution comparison containing individual values and a corresponding dissolution study report were requested. The applicant provided comparative dissolution profiles for 300/25 and 150/12.5 mg strengths in three different dissolution media without a surfactant. Additionally, dissolution study on different hydrodynamic conditions was performed to show the similarity of dissolution profiles. The justification was found acceptable.

Analytical methods used for the finished product control were sufficiently described and appropriately validated according to the guideline CPMP/ICH/381/95.

Batch analysis results of three pilot batches per strength confirming compliance with the specification and consistency of manufacture have been submitted.

Stability of the Product

The stability studies are carried out in accordance with the current CHMP/ICH guidelines. All tests were carried out by validated, stability indicating analytical methods. In addition to release specification, water content and hardness are monitored for information, without any established limit.

Film-coated tablets of all three strengths were placed on stability, three pilot batches per strength. The applicant is using a matrixing approach as per the relevant guideline, CPMP/ICH/4104/00.

Accelerated studies (40ºC/75% RH) have been completed for all monitored batches. At present 12 months of long-term stability results (at 25ºC/60% RH) are available. No significant changes or trends were observed so far. All results comply with the shelf-life specifications.

The stability studies are ongoing. The last time point in the stability protocol will be 60 months. Production scale batches will be tested post-approval.

In general, the results support the shelf-life and storage conditions as defined in the SmPC.

In accordance with EU GMP guidelines[2], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

[2] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

2.2.5. Discussion on chemical, and pharmaceutical aspects

Initial major objection on pharmacokinetics, related to dissolution, was satisfactorily solved by the applicant. Dissolution of the product was thoroughly examined and described. The quality of the product is considered satisfactory.

2.2.6. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.3. Non-Clinical aspects

Since this application is a generic application referring to the originator product CoAprovel, no new non-clinical studies on the pharmacology, pharmacokinetics and toxicology of irbesartan and hydrochlorothiazide have been undertaken. Both irbesartan and hydrochlorothiazide are widely used well-known active substances. Their pharmacodynamic, pharmacokinetic and toxicological properties are well characterised. No further studies are required and the applicant has justified why no such data were provided.

No Environmental Risk Assessment was submitted, which is considered acceptable and in line with current guidelines.

2.4. Clinical Aspects

Introduction

This application is a generic application, therefore, demonstration of therapeutic equivalence is shown by means of pharmacokinetic bioavailability studies. Consequently, new clinical studies are neither required nor submitted.

The safety and efficacy profile of irbesartan and hydrochlorothiazide has been demonstrated in several clinical trials, details of which can be found in the EPAR of the reference product CoAprovel. In addition, there is long-term post-marketing experience contributing to the knowledge of the clinical use of this product.

In order to prove bioequivalence of the three strengths, the applicant has performed 2 bioequivalence studies with the 300/25 mg and 300/12.5 mg strength, respectively, and has applied for a biowaiver of a proportional formulation (150/12.5 mg).

GCP

The Clinical trials were performed in accordance with GCP and the ethical requirements of Directive 2001/20/EC as claimed by the applicant.

Pharmacokinetics

The applicant has submitted two single-dose fasted-state bioequivalence studies that were sponsored by Krka d.d.:

Randomized, open-label, 2-way crossover study of irbesartan-hydrochlorothiazide 300 mg/25mg and CoAprovel 300mg/25 mg film-coated tablet in healthy volunteers.

Randomized, laboratory-blinded, 2-way crossover study of irbesartan-hydrochlorothiazide 300/12.5 mg and CoAprovel 300mg/12.5mg film-coated tablets in healthy volunteers.

The pre-study and in-study validation of the analytical method in the two studies for both analytes is satisfactory and in accordance with the current guidelines.

The LLOQ for both drugs is lower than 5% of the minimum Cmax. Therefore, in case of a carry-over effect was present it would have been detected.

Results

The pharmacokinetic analysis is adequate for both studies. The statistical analysis performed is parametric, except for Tmax, in accordance with the Guideline on the investigation of bioequivalence.

Study for the 300mg/25mg strength

Based on the statistical analyses the 90% confidence intervals calculated for AUC(0-t), AUC(0-inf) and Cmax of both drugs were inside the normal range of acceptability (0.80 – 1.25).

Table A: Ratios, 90% geometric confidence intervals and intra-subject CVs (%) for AUC_{0-t}, AUC_{0-inf}, and C_{max} for irbesartan (N = 37)

	AUC_{0-t}	**AUC_{0-inf}**	**C_{max}**
Ratio[1]	96.99%	97.00%	103.62%
90 % Geometric C.I.[2]	93.27 % to 100.86 %	92.61 % to 101.58 %	96.87 % to 110.84 %
Intra-Subject CV	9.98 %	11.80 %	17.27 %

[1] Calculated using least-squares means according to the formula: $e^{(A-B)}$ X 100.
[2] 90% Geometric Confidence Interval using ln-transformed data.

Table B: Ratios, 90% geometric confidence intervals and intra-subject CVs (%) for AUC_{0-t}, AUC_{0-inf}, and C_{max} for hydrochlorothiazide (N = 37)

	AUC_{0-t}	**AUC_{0-inf}**	**C_{max}**
Ratio[1]	104.24%	103.19%	110.02%
90 % Geometric C.I.[2]	96.95 % to 112.09 %	97.61 % to 109.09 %	97.57 % to 124.07 %
Intra-Subject CV	18.63 %	14.22 %	31.31 %

[1] Calculated using least-squares means according to the formula: $e^{(A-B)}$ X 100.
[2] 90% Geometric Confidence Interval using ln-transformed data.

Study for the 300mg/12.5 mg strength

Based on the statistical analyses submitted by the applicant the 90% confidence intervals calculated for AUC(0-t), AUC(0-inf) and Cmax of both drugs were inside the normal range of acceptability (0.80 – 1.25) (see tables below).

Irbesartan

PARAMETER	TEST		REFERENCE	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (ng/mL)	3888.2	38.4	4047	44.7
ln (C_{max})	8.2030	4.3	8.2315	4.5
T_{max} (hours)*	0.75	50.7	1	51.7
AUC_T (ng h/mL)	21050.6	41.6	19916.9	47.5
ln (AUC_T)	9.8869	3.6	9.8151	4
AUC_∞ (ng h/mL)	22093.2	42	21345.0	48.2
ln (AUC_∞)	9.9323	3.7	9.8834	4
$AUC_{T/\infty}$ (%)	95.26	3.9	93.78	4.2
K_{el} ($hours^{-1}$)	0.0705	44	0.064	49.9
$T_{1/2el}$ (hours)	11.73	43.7	12.96	41

* median is presented

PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	16.1	3652.1	3757.4	97.20	91.50	103.24
AUC_T	11.7	19670.4	18309.0	107.44	102.80	112.28
AUC_∞	11.6	20759.6	19809.9	104.79	100.07	109.74

* units are ng/mL for C_{max} and ng·h/mL for AUC_T and AUC_∞

Hydrochlorothiazide

PARAMETER	TEST		REFERENCE	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (ng/mL)	84.04	23.7	84.57	31.4
ln (C_{max})	4.3999	6	4.3871	7.5
T_{max} (hours)*	1.75	35.7	1.5	33.3
AUC_T (ng h/mL)	503.66	19.7	481.51	20.6
ln (AUC_T)	6.2036	3.1	6.1543	3.6
AUC_∞ (ng h/mL)	527.81	19.5	506.32	20.1
ln (AUC_∞)	6.2511	3	6.2069	3.3
$AUC_{T/\infty}$ (%)	95.38	1.6	94.91	2.6
K_{el} ($hours^{-1}$)	0.0774	12.3	0.0744	12.9
$T_{1/2el}$ (hours)	9.09	12.7	9.49	15.3

* median is presented

PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	22.1	81.44	80.41	101.29	93.26	110.00
AUC_T	15.1	494.53	470.72	105.06	99.27	111.18
AUC_∞	13.5	518.57	496.14	104.52	99.34	109.97

* units are ng/mL for C_{max} and ng·h/mL for AUC_T and AUC_∞

Pharmacodynamics

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

Safety data

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

Post marketing experience

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

2.4.1. Conclusions on clinical aspects

Bioequivalence between the test product and the reference product has been shown for the 300/25 mg and 300/12.5 mg strengths. Extrapolation of the evidence obtained in the bioequivalence study for the 300/25 mg strength to the proportional strength of 150/12.5 mg is possible. Bioequivalence was shown with the highest strength, kinetics is linear, this lower strength is qualitatively identical and quantitatively proportional in composition, and dissolution profiles are similar at 50 rpm with the paddle apparatus in media without surfactant at pH 1.2, 4.5 and 6.8.

Based on the presented bioequivalence studies Ifirmacombi is considered bioequivalent with CoAprovel.

2.5. Pharmacovigilance

PSUR

The PSUR submission schedule should follow the PSUR submission schedule for the reference medicinal product. The PSUR of the reference product is on a 3-yearly cycle and the next data lock point is 29 September 2013.

Description of the Pharmacovigilance system

The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements. The MAH must ensure that the system of pharmacovigilance presented in

Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management plan
Not applicable

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

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.*

Combined Package Leaflet
The QRD plenary considered the request of the applicant to use a combined Package Leaflet as acceptable.

2.6. Benefit/risk assessment and recommendation

Overall conclusion and Benefit/risk assessment

The application contains adequate quality, non clinical and clinical data and bioequivalence has been shown. A benefit/risk balance 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 balance of Ifirmacombi in the treatment of essential hypertension in adult patients whose blood pressure is not adequately controlled on irbesartan or hydrochlorothiazide alone was favourable and therefore recommended the granting of the marketing authorisation.