CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Irbesartan HEXAL comp 300/25 mg and Irbesartan HEXAL comp 150/12.5 mg, film-coated tablets Hexal AG, Germany

irbesartan/hydrochlorothiazide

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1581/001+003/DC
Registration number in the Netherlands: RVG 103798, 103797

20 May 2010

Pharmacotherapeutic group:	angiotensin II antagonists and diuretics
ATC code:	C09DA04
Route of administration:	oral
Therapeutic indication:	essential hypertension in adult patients whose blood pressure is not adequately controlled on irbesartan or hydrochlorothiazide alone
Prescription status:	prescription only
Date of authorisation in NL:	22 March 2010
Concerned Member States:	Decentralised procedure with DE, LU
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Irbesartan HEXAL comp 300/25 mg and Irbesartan HEXAL comp 150/12.5 mg, film-coated tablets from Hexal AG. The date of authorisation was on 22 March 2010 in the Netherlands.

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

A comprehensive description of the indications and posology is given in the SPC.

Irbesartan/hydrochlorothiazide is a combination of an angiotensin II receptor antagonist, irbesartan, and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.
Irbesartan is a potent, orally active, selective angiotensin II receptor (AT_1 subtype) antagonist. It is expected to block all actions of angiotensin II mediated by the AT_1 receptor, regardless of the source or route of synthesis of angiotensin II. The selective antagonism of the angiotensin II (AT_1) receptors results in increases in plasma rennin 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 which acts as by inhibiting fluid-expelling and blood pressure-lowering agent which increase the tubular re-absorption of sodium in the cortical diluting segment.
It increases the urinary excretion of sodium and chloride and, to a lesser degree, the excretion of potassium and magnesium, thus increasing diuresis and exerting an anti-hypertensive effect.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product CoAprovel 300/25 mg and 150/12.5 mg tablets which have been registered through the centralised procedure by Sanofi Pharma Bristol-Myers Squibb SNC since 15 October 1998 (150/12.5 mg) and 28 August 2006 (300/25 mg). Further information can be found in the EPAR of CoAprovel (http://www.ema.europa.eu/htms/human/epar/).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the 300/25 mg product is compared with the pharmacokinetic profile of the reference product CoAprovel 300/25 mg tablets, registered in the European Union. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic products can be used instead of their reference products.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substances

Irbesartan
General information
The first active substance is irbesartan, an established active substance described in the US Pharmacopoeia. (USP*). Irbesartan is a white to almost white powder. The active substance is practically insoluble in water at different pHs. In literature two polymorphic forms are known. Polymorphic form A is used.

The Active Substance Master File (ASMF) procedure is used for both suppliers of the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
For both manufacturers, the active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents. No class 1 solvents or heavy metal catalysts are used in the process.

Quality control of drug substance
The drug substance specification has been established in-house by the MAH. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 full-scale batches from both suppliers.

Stability of drug substance
For one supplier, stability data on the active substance have been provided for 3 full-scale batches stored at 25°C/60% RH (9 months) and 40°C/75% RH (6 months). Based on the results, the proposed retest period of 12 months without additional storage requirements could be granted.
For the other supplier, stability data on the active substance have been provided for 3 full-scale and 11 pilot-scale batches stored at 25°C/60% RH (up to 60 months) and 40°C/75% RH (6 months). All parameters tested were considered to be stable, as no up or downward trends were observed in any of the examined parameters under both long-term and accelerated conditions. The proposed retest period of 36 months without additional storage requirements could therefore be granted.

** USP is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the USA.*

Hydrochlorothiazide
General information
The second active substance is hydrochlorothiazide, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or almost white crystalline powder,

which is very slightly soluble in water, soluble in acetone and sparingly soluble in ethanol. Polymorphism is not known for hydrochlorothiazide. A requirement for particle size has been set.

The CEP procedure is used for both suppliers of the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The MAH's drug substance specification is in line with the CEP, with additional requirements for residual solvents and impurities. The specifications are in line with the Ph.Eur. monograph. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 2 full-scale batches from each supplier.

Stability of drug substance
For one supplier, a retest period of 3 years could be granted. For the other supplier, a retest period of 5 years is applicable. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Irbesartan HEXAL comp 150/12.5 mg is an apricot, oval biconvex film-coated tablet, debossed with 150H on one side.
Irbesartan HEXAL comp 300/25 mg is a dark pink, oval biconvex film-coated tablet, debossed with 300 on one side and 25H on other side.

The film-coated tablets are packed in Al/Al blisters, PVC/PVDC/Al blisters and HDPE bottles with a PP screw cap and silica gel desiccant.

The excipients are:
tablet core - microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, colloidal anhydrous silica, hypromellose 3 mPas, silicified microcrystalline cellulose, magnesium stearate.
film-coating - hypromellose 6 mPas, hydroxypropylcellulose, macrogol 6000, lactose monohydrate, titanium dioxide (E171), talc, ferric oxide red (E172), ferric oxide yellow (E172) (150/12.5 mg only), ferric oxide black (E172) (300/25 mg only).

The tablet cores of the 2 strengths are manufactured dose proportionally.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were the characterisation of the originator product, comparative dissolution studies and optimising the manufacturing process. Batches from different European markets (FR, DE and UK) for both the 150/12.5 mg and 300/25 mg innovator tablets show similar dissolution profiles. The tablets used for the BE studies have been manufactured according to the final manufacturing process. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process includes granulation, drying, sieving, blending, compression and coating of the tablets. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 3 full-scale batches of 300/25 mg and 4 full-scale batches of 150/12.5 mg. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with the Ph.Eur. or USP. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, uniformity of dosage units, identification, assay, water content, dissolution, related substances, residual solvents and microbial limits. Except for impurities, water content and assay, the release and shelf-life requirements/limits are identical. The specifications are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 3 full-scale batches of both strengths, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for three full scale batches of both strengths, stored at 25°C/60% RH (up to 18 months), 30°C/65% RH (up to 12 months, only for PVC/PVDC/Al blisters) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PVDC/Al blisters, Al/Al blisters and HDPE bottles. No significant changes are observed during long term and intermediate storage conditions. For tablets packed in PVC/PVDC/Al blisters, a significant increase of one impurity is found at accelerated storage conditions. No significant changes were seen in the other packaging materials at this storage condition. The proposed shelf life of 24 months is justified for the drug product in all packaging materials, with the additional storage requirement to store in the original package in order to protect from moisture. The drug product packed in PVC/PVDC/Al blisters should be stored below 30°C.
The MAH committed to perform long-term stability testing at least throughout the proposed shelf life period (24 months). The intermediate stability study will be continued up to 12 months.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Except for lactose, there are no substances of ruminant animal origin present in the product, nor have any been used in the manufacturing of this product. For lactose, compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non clinical aspects

This product is a generic formulation of CoAprovel, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of irbesartan or hydrochlorothiazide released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Irbesartan and hydrochlorothiazide are well-known active substances with established efficacy and tolerability.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Irbesartan HEXAL comp 300/25 mg is compared with the pharmacokinetic profile of the reference product CoAprovel 300/25 mg tablets (Bristol-Meyer Squib SNC, France). The French reference product is acceptable, as CoAprovel is registered through the centralised procedure.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, two-way crossover bioequivalence study was carried out under fasted conditions in 38 healthy male subjects, aged 24-54 years with a BMI of 19-28. Each subject received a single dose (300/25 mg) of one of the 2 irbesartan/hydrochlorothiazide formulations. The tablet was orally administered with 240 ml water after an overnight fast of 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 36, 48 and 72 hours after administration of the products.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Thirty-eight subjects were dosed in the first period. One subject voluntarily withdrew from the study prior to period 2 check-in for personal reasons. Another subject voluntarily withdrew from the study prior to period 2 check-in due to adverse events (sore throat, tiredness, throat infection). Thirty-six (36) subjects were dosed in period 2. One subject voluntarily withdrew from the study in period 2 for personal reasons. The remaining 35 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of irbesartan under fasted conditions.

Treatment N=35	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	19.90 ± 5.80	20.50 ± 6.25	3.95 ± 1.12	1.5 (0.67-5.0)	12.9 ± 5.3
Reference	20.90 ± 7.17	21.65 ± 7.64	3.45 ± 1.01	1.5 (0.67-5.0)	14.6 ± 8.6
***Ratio (90% CI)**	0.96 (0.90-1.02)	0.95 (0.89-1.02)	1.14 (1.07-1.20)	-	-
CV (%)	17	17	14	-	-

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of hydrochlorothiazide under fasted conditions.

Treatment N=35	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1031 ± 245	1064 ± 254	168 ± 53	1.75 (1.0-4.0)	10.6 ± 1.5
Reference	1094 ± 227	1123 ± 239	184 ± 44	1.5 (1.0-4.0)	10.2 ± 1.3
***Ratio (90% CI)**	0.94 (0.90-0.98)	0.94 (0.91-0.98)	0.90 (0.84-0.97)	-	-
CV (%)	10	10	18	-	-

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of irbesartan and hydrochlorothiazide under fasted conditions, it can be concluded that Irbesartan HEXAL comp 300/25 mg and CoAprovel 300/25 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Irbesartan/hydrochlorothiazide may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of irbesartan/hydrochlorothiazide combination. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Extrapolation to 150/12.5 mg tablet
According to the CPMP guideline 'Note for guidance on the investigation of bioavailability and bioequivalence' (CPMP/EWP/QWP/1401/98), a bioequivalence study investigating only one tablet strength may be acceptable if all of the following conditions are fulfilled:

- the pharmaceutical products are manufactured by the same manufacturer and process
- the pharmacokinetics has been shown to be linear over the therapeutic range
- the qualitative composition of the different strengths is the same
- the ratio between amounts of active substance and excipients is the same
- the dissolution profile should be similar under identical conditions for the additional strengths and the strength of the biobatch.

Since all these conditions are met, the results of the bioequivalence study performed with the 300/25 mg tablet apply to the 150/12.5 mg strength as well.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan
In view of the existing knowledge and experience with the active substances irbesartan and hydrochlorothiazide, the available data and the known risk-benefit profile, it is accepted that the MAH will perform standard pharmacovigilance activities as described in volume 9 of *The rules governing medicinal*

products in the European Union. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. An additional Risk Management Plan and Risk Minimisation Plan are not required at the moment. If, in the future, new data suggest differently the submission of a Risk Management Plan and a Risk Minimisation Plan can be necessary.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with the latest recommendations of the Pharmacovigilance Working party 'Angiotensin Converting Enzyme (ACE) inhibitors & Angiotensin II Receptor Antagonists (AIIRAs): Use during pregnancy & lactation; Final SPC and PIL wording agreed by PhVWP October 2008'.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of two rounds with 10 participants each. There will be 16 questions related to content of PIL and 3 related to the structure/appearance of PIL. In the first round, information was found and a correct explanation provided by at least 90% of the subjects for 15 of the 16 questions. One question relating to the ingredient lactose was found and a correct explanation provided by only 8 subjects. An additional cross reference in section 6 directing the patient to section 2 'Important information about some of the ingredients' was added to the leaflet. In round 2, the revision had a positive impact in that information was found and explained correctly by all 20 subjects tested for this question. Information was found and a correct explanation provided by all subjects for the remaining questions. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Irbesartan HEXAL comp 300/25 mg and Irbesartan HEXAL comp 150/12.5 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of CoAprovel 300/25 mg and 125/12.5 mg film-coated tablets. CoAprovel is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other irbesartan/hydrochlorothiazide containing products.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Irbesartan HEXAL comp 300/25 mg and Irbesartan HEXAL comp 150/12.5 mg, tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 23 November 2009. Irbesartan HEXAL comp 300/25 mg and Irbesartan HEXAL comp 150/12.5 mg, film-coated tablets were authorised in the Netherlands on 22 March 2010.

The first PSUR will cover the period from November 2009 to August 2012. The PSUR submission cycle is 3 years.

The date for the first renewal will be: 23 May 2013.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to perform long-term stability testing at least throughout the proposed shelf life period (24 months). The intermediate stability study will be continued up to 12 months.

Regulatory

- The MAH committed to shall make an application for the intermediate strength 300/12.5 mg with at least HU as CMS.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached