CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Irbesartan/Hydrochloorthiazide 1A Pharma 300/12,5 mg film-coated tablets 1A Pharma, 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/1582/002/DC
Registration number in the Netherlands: RVG 107108

15 August 2011

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 2011
Concerned Member States:	Decentralised procedure with DE and HU
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/Hydrochloorthiazide 1A Pharma 300/12,5 mg film-coated tablets, from 1A Pharma. The date of authorisation was on 22 March 2011 in the Netherlands.

The product is indicated for 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.

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. 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, coadministration of irbesartan tends to reverse the potassium loss associated with these diuretics.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product CoAprovel 300/12.5 mg tablets (EU License EU/1/98/086/016-022) which have been registered through the centralised procedure by Sanofi Pharma Bristol-Myers Squibb SNC since 15 October 1998. 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 one bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product CoAprovel 300/12.5 mg tablets, registered in France. 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. This generic product can be used instead of its reference product.

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 generic medicinal products.

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 this product type 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
irbesartan an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Irbesartan is practically insoluble in water. Irbesartan does not exhibit stereochemistry and exists in two polymorphic forms (A and B).

The Active Substance Master File (ASMF) procedure is used for this 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

Manufacture
The manufacturing process consists of three steps. The organic solvents used in the last steps of the synthesis have been described. No class 1 organic solvents are used in the process. The active substance has been adequately characterized and acceptable specifications have been adopted for the staring material, solvents and reagents.

Quality control of drug substance
The drug substance specification has been established in-house by the MAH.

Stability of drug substance
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). The batches were adequately stored. All parameters tested are considered to be stable, no up or downward trends are observed in any of the examined parameters under both, long-term and accelerated conditions. The proposed re-test period of 36 months without additional storage requirements is justified.

Hydrochlorothiazide

General information
Hydrochlorothiazide is an established active substance described in the European Pharmacopoeia (Ph. Eur.). The active substance is very slightly soluble in water.

The CEP procedure is used for 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, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Manufacturing process
The manufacturing process is covered by the CEP.

Quality control of drug substance
The MAH's drug substance specification is in line with the Ph.Eur. monograph and the requirements of the CEP, with additional requirements for particle size. Batch analytical data demonstrating compliance with the drug substance specification have been provided on two full-scale batches from both suppliers.

Stability of drug substance
The active substance from both suppliers is stable for respectively three and five years when adequately stored. 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/Hydrochloorthiazide 1A Pharma 300/12,5 mg – are apricot, oval biconvex film-coated tablets, debossed with *300H* on one side.
The 300/12.5 mg tablets are a line extension to the already authorized irbesartan/hydrochlorothiazide 150/12.5 (NL license RVG 103784) and 300/25mg (NL license RVG 103788) film-coated tablets.

The excipients are:
Tablet core - microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, colloidal anhydrous silica, hypromellose, silicified microcrystalline cellulose and magnesium stearate.

Film-coating - hypromellose hydroxypropylcellulose, macrogol 6000, lactose monohydrate, titanium dioxide (E171), ferric oxide (yellow and red) (E172), and talc

The tablets are packed into PVC/PVDC/Al blisters, Al/Al blisters, or HDPE bottles with a PP screw cap and silica gel desiccant.

The excipients and packaging are usual for this type of dosage form.

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 optimizing of the manufacturing process. The batch used for the bioequivalence studies has been manufactured according to the finalized formulation and manufacturing process. The pharmaceutical development of the product has been adequately performed.

Container closure system
Al/Al-blister
The Al/Al-blister packaging contains of a layer of soft aluminium foil with a PVC inner surface and a layer of hard aluminium foil with an inner thermoplastic lacquer based on PVC. Specifications for both aluminium foils and a certificate of analysis, with IR spectrum, are included in the dossier.
The PVC inner surface complies with Directive 2002/72/EC and Ph.Eur. 3.1.11.

PVC/PVdC-Al blister
The blister contains of a layer of transparent PVC/PVdC hard foil, suitable for thermoforming, with a PVDC inner surface and a hard aluminium foil layer with a thermoplastic inner lacquer based on PVC. Specifications for both foils are included in the dossier, together with a certificate of analysis and IR spectrum for identification. The PVC/PVdC-blister complies with Directive 2002/72/EC and with Ph.Eur. 3.1.11.

HDPE bottles
The bottles are white round HDPE bottles sized 40, 75, 200, 250 and 500ml and are closed with a white child resistant polypropylene screw cap (33, 38 and 53mm). Drawing, specifications and certificates of analysis are included in the dossier. The HDPE bottles comply with Directive 2002/72/EC and the material with Ph.Eur. 3.1.3 monograph on polyolefines. The screw caps comply with Directive 2002/72/EC and Ph.Eur. 3.1.6 monograph (polypropylene for containers and closures for parenteral preparations and ophthalmic preparations). The child resistant properties of the screw-caps were not tested, this is acceptable since it is not claimed in the SPC. As the HDPE bottles have been described in sufficient detail.

Desiccant canister
A silica gel desiccant canister, containing 1 g of silica gel is included in the HDPE bottles. The canister complies with Directive 2002/72/EC.

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

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. The product is manufactured using conventional manufacturing techniques.

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 related substances, 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, demonstrating compliance with the release specification.

Microbiological attributes
The test for microbial contamination is included as a part of finished product specification to check the microbiological quality of the drug product. Microbiological quality was tested at release and during stability studies and compliance with the requirements for non-aqueous preparations for oral use of Ph.Eur. monograph 5.1.4 was demonstrated.

Stability tests on the finished product
Stability data on the product has been provided on five full-scale batches stored at 25°C/60% RH (up to 24 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 "*Store in the original package in order to protect from moisture*" and only for the PVC/PVdC-Al blister pack "*Do not store above 25°C* ".

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, so a theoretical risk of transmitting TSE can be excluded. 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.

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

II.2 Non clinical aspects

This product is a generic formulation of CoApprovel, 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 one bioequivalence study in which the pharmacokinetic profile of the test product Irbesartan/Hydrochloorthiazide 1A Pharma 300/12,5 mg film-coated tablets (1A Pharma, Germany) is compared with the pharmacokinetic profile of the reference product CoAprovel 300/12.5 mg tablets (Bristol-Meyer Squib SNC, France).

The choice of the reference product
CoAprovel 300/12.5 mg tablets are registered via the centralised procedure and hence are presumed to be identical in all member states of the EEA.

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

Bioequivalence study
A single dose, two-way crossover bioequivalence study was carried out under fasted conditions in 38 healthy male volunteers, aged 20-44 years (with a BMI of 19 – 28 kg/m^2). Each subject received a single dose (300 mg irbesartan, 12.5 mg hydrochlorothiazide) of one of the 2 irbesartan / hydrochlorothizide formulations. A randomization scheme was provided. The tablet was orally administered with 240 ml water after an overnight fasting period of 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected predose and at 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, 48 and 72 hours after administration of the products.
The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

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. 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.

Results

No serious adverse events (Aes) were reported during the conduct of this study. None of the AEs had a significant impact on the safety of the subjects or on the integrity of the study results. Thirty-eight (38) subjects were dosed in Period. One subject withdrew before the second period for personal reasons. Thirty-seven subjects 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 = 37	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	15.69 ± 6.14	17.81 ± 6.25	3.87 ± 1.07	1.25 (0.5 – 5.0)	12.4 ± 6.6
Reference	16.35 ± 5.83	17.90 ± 5.82	3.38 ± 1.08	1.3 (0.5 – 5.0)	12.2 ± 4.7
***Ratio (90% CI)**	0.94 (0.89 – 0.99)	---	1.15 (1.08 – 1.23)	---	---
CV (%)	13.4	---	16.2	---	---

$AUC_{0-\infty}$ 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 = 37	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	489 ± 107	531 ± 104	79.8 ± 19.8	1.75 (0.67 – 4.0)	9.8 ± 1.3
Reference	489 ± 104	532 ± 104	80.2 ± 22.2	1.75 (1.0 – 3.0)	9.6 ± 1.4
***Ratio (90% CI)**	1.00 (0.95 – 1.04)	---	1.00 (0.93 – 1.07)	---	---
CV (%)	11.4	---	19.2	---	---

$AUC_{0-\infty}$ 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} for both active substances 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/Hydrochloorthiazide 1A Pharma 300/12,5 mg film-coated

tablets and the CoAprovel 300/12.5 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

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

The MAH submitted a statement on the absence of a Risk Management Plan, and indicated that the current application concerns a generic product, for which the active ingredients have been in use for many years, and have a well-established safety profile. Routine Pharmacovigilance activities in accordance with EU regulations will be undertaken whilst the product are authorized. As the safety profile of the drug is well-established, a Risk Minimisation Plan is not considered necessary.
The reasoning of the MAH is accepted. At present, no risk management plan is needed.

Product information

Readability test

The MAH has shown that the findings of the user test on the in-pack leaflet for Irbesartan/HCTZ 300 mg / 25 mg film-coated tablets (NL license RVG 103788, successfully tested) can be bridged to the in-pack leaflet for Irbesartan/HCTZ 300 mg / 12.5 mg film-coated tablets.
This conclusion is reached on the grounds that:

- The product is prescription medicines containing the same active substances, irbesartan and hydrochlorotiazide.
- It has the same indication and the same target population.
- The expected side effect profiles are the same.
- The in-pack leaflets are similar in terms of design, content and writing style.
- The new layout was already successfully tested in several readability tests.

The MAH's conclusion is endorsed by the member states. No further testing is needed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Irbesartan/Hydrochloorthiazide 1A Pharma 300/12,5 mg film-coated tablets have a proven chemical-pharmaceutical quality and are a generic form of CoAprovel 300/12.5 mg 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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Irbesartan/Hydrochloorthiazide 1A Pharma 300/12,5 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 7 March 2011. Irbesartan/Hydrochloorthiazide 1A Pharma 300/12,5 mg film-coated tablets is authorised in the Netherlands on 22 March 2011.

The first PSUR will cover the period from approval to 31 August 2012, after which 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 has committed to report the 18-month and 24-month long-term stability data for the ongoing batches. In addition, the MAH should also submit the 12-month stability data.

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