CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Dazirok 150/12.5 mg, 300/12.5 mg, and 300/25 mg tablets
Laboratorios Liconsa S.A., Spain

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/1683/001-003/DC
Registration number in the Netherlands: RVG 104736-8

25 March 2011

Pharmacotherapeutic group:	angiotensin II antagonists and diuretics
ATC code:	C09DA04
Route of administration:	oral
Therapeutic indication:	essential hypertension in n adult patients whose blood pressure is not adequately controlled on irbesartan or hydrochlorothiazide alone
Prescription status:	prescription only
Date of authorisation in NL:	16 February 2011
Concerned Member States:	Decentralised procedure with AT, DE, and the UK
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 Dazirok 150/12.5 mg, 300/12.5 mg, and 300/25 mg tablets, from Laboratorios Liconsa S.A. The date of authorisation was on 16 February 2011 in the Netherlands. The product is indicated for the treatment of essential hypertension 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
Irbesartan is a potent, orally active, selective angiotensin-II receptor (AT1 subtype) antagonist. 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.

HCTZ
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.

Combined product
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 an overall placebo-subtracted systolic/diastolic reductions of up to 13.6/11.5 mm Hg.

This decentralised procedure concerns a generic application claiming essential similarity with CoAprovel 150 mg/12.5 mg tablets (EU License EU/1/98/086/001-003) which have been registered through a centralised procedure by Sanofi Pharma Bristol-Myers Squibb SNC since 1998.

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 two bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference products Coaprovel 300/12.5 mg tablets and Coaprovel

300/25 mg coated tablets, both registered in Spain. 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.

This decentralised procedure concerns a so-called fixed dose application. Fixed dose combinations contain active substances from medicinal products already authorised in the EU but not hitherto used in combination for therapeutic purposes. In these kind of applications the results of new pre-clinical tests or new clinical trials relating to that combination are provided. However, it is not necessary to provide pre-clinical and clinical data relating to each individual active substance. Therefore, no new pre-clinical and clinical studies were conducted.

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 substance
The active substances are irbesartan and hydrochlorothiazide. Irbesartan is an established active substance described in the Ph.Eur.* and USP* and exhibits two polymorph forms, of which Form A is employed in the manufacturing of irbesartan/hydrochlorothiazide tablets. Irbesartan is insoluble at different pH's and has no chiral centers.
Hydrochlorothiazide is a well known active substance, described in the European Pharmacopoeia and is very slightly soluble in water, soluble in acetone and sparingly soluble in ethanol. Hydrochlorothiazide shows polymorphism, Form I is used.

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

The CEP procedure is used for hydrochlorothiazide. 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 suitablity 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.

<u>Manufacturing process</u>
Irbesartan is manufactured in a four step process. A flow chart and short description of the manufacturing process was included. The solvents used during the manufacturing process haven been described.The structure of Irbesartan has been adequately elucidated.

Quality control of drug substance
Irbesartan specification is in line with the Ph.Eur., with additional requirements for nickel and palladium, polymorphism, residual solvents and particle size. 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 three production scaled batches.
Hydrochlorothiazide is considered adequately controlled by the CEP. No additional requirements are specified, but water will be used as solvent in the last step of synthesis.

Stability of drug substance
Irbesartan - Stability data on the active substance have been provided for five production scaled batches and two pilot scaled batches stored at 25°C/60% RH (36 months data for five batches) and 40°C/75% RH (6 months). Additional stability results of three batches manufactured from the alternative starting material and stored for 3 months at both accelerated and long term conditions have been included. The batches were adequately stored. At accelerated storage conditions no changes were observed. At long term storage conditions only a slight increase in water content is seen after two or three years. The claimed shelf-life of three years is justified. A photostability study has been included in the DMF and the claimed storage conditions are thus considered justified.
Hydrochlorothiazide - A retest period of 5 years is approved by the CEP for the active substance when stored under the proposed conditions.

** Ph.Eur. and USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU and USA respectively.*

Medicinal Product

Composition
Dazirok 150/12.5 mg – are white, cylindrical, biconvex tablets, embossed *1H1* on one side.
Dazirok 300/12.5 mg – are white, oblong, biconvex tablets, embossed 1H12 on one side.
Dazirok 300/25 mg – are white, oblong, biconvex tablets, embossed *1H25* on one side.

The tablets containing 300 mg Irbesartan are dose proportional to the 150 mg strength. The tablets are packed in PVC-PE-PVDC (triplex) /Aluminium blisters.
The following excipients are used: povidone, magnesium stearate, microcrystalline cellulose, sodium croscarmellose, lactose monohydrate, colloidal anhydrous silica, hydrogenated castor oil and maize starch.
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 intention was to develop a formulation by mimicking as closely as possible the reference product and the latter was therefore investigated. The study included an evaluation of the following parameters: appearance, hardness, dimensions, weight, disintegration, residual water content, dissolution and assay content. Comparative dissolution data has been submitted in various pHs over an acceptable range. The test products and reference product are considered similar on the basis of dissolution profiles. The MAH has adequately discussed the influence of particle size of the drug substances on the dissolution profile but is requested to include a requirement in the specification for hydrochlorothiazide. It was demonstrated that sink conditions are present for hydrochlorothiazide, but not for Irbesartan. This is not considered to be product related, but due to the substance itself.

Manufacturing process
Wet granulation is employed. The process consist of four steps namely kneading, drying of the kneaded granulate and sieving, final mixing and tabletting. In-process controls during the tabletting include nominal weight, friability and disintegration.
The manufacturing process has been adequately described, although more details regarding sieve sizes and mixing times will be finalized after validation. The 300/12.5mg contains less then 2% active

substance. Full scale validation for one site is performed for the 300/12.5mg product, full scale validation for another site should be provided.

Quality control of drug product
The following parameters are controlled: appearance, uniformity of dose, loss on drying, dissolution, identification, assay, related substances, microbial quality. Release and shelf-life specifications are the same for all parameters. Tests for disintegration, water content and hardness have been included as in process controls. The drug product specification is acceptable. The analytical methods have been adequately described and validated. Batch analysis for all three respective strengths have been included and all results confirm compliance with the final product specifications.

Container closure system
Certificates of compliance of the aluminium and lacquer with Directive 2002/72/EC and Ph.Eur. 3.1.11 have been included, as well as an IR spectrum. Certificates of compliance with Directive 2002/72/EC have also been included for PVC and PE and PVDC. This is acceptable.

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, since some excipients may tend to support microbial growth. Microbiological control is performed at the start of the study and at the end of each phase (6 months: 40ºC/75%RH, 12 months: 30ºC/65%RH, and 36 months: 25°C/60%RH). Since *Escherichia coli* has been shown to be absent at the start of the stability study, confirmation of its absence during the stability study is not considered to be required as the sample cannot be contaminated during storage.

Stability tests on the finished product
Stability data has been provided for three pilot scale batches of the 150/12.5 mg and 300/12.5 mg strength and for two batches of the 300/25 mg strength from one manufacturing site. In addition, three batches of each strength are subjected to stability studies (long term, intermediate and accelerated conditions) from the other site. Except for a significant decrease in dissolution of Irbesartan (max. of 8.3%), no significant changes are observed in any of the other parameters tested during the stability trials performed with the 150/12.5 mg and 300/12.5 mg strengths. In view of the current results a shelf-life of 36 months was granted for these two strengths.
Since data of only 18 months at long-term and 6 months at accelerated conditions have been provided for the 300/25 mg strength a shelf-life of 24 months is justified for this strength. No special storage conditions are required for any of the strengths.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
According to the available documentation provided by the respective suppliers of the raw materials, none of the ingredients are of animal origin, except for lactose monohydrate. This excipient is a milk derivative produced by DMV International who guarantees the absence of the risk of transmission of agents of animal spongiform encephalopathy.

Several post-approval commitments have been made by the MAH with regard to quality. Please see page 11.

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 both a well-known active substances with established efficacy and tolerability.

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test products Dazirok 300/12.5 mg and 300/25 mg (Laboratorios Liconsa S.A., Spain) are compared with the pharmacokinetic profile of the reference products Coaprovel 300/12.5 mg (Sanofi Pharma Bristol-Myers Squibb SNC, Spain) and Coaprovel 300/25 mg tablets (Sanofi Aventis SAU, Spain).

Coaprovel 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.

Irbesartan and 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 or 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.

Bioequivalence study with 300/12.5 mg strength
A single-dose, open-label (with two sequences and two periods), randomized bioequivalence study was carried out under fasting conditions in 24 healthy (12 male and 12 female) volunteers, aged 18-26 years. Each subject received a single dose (300 mg irbesartan, 12.5 mg hydrochlorothiazide) of one of the 2 irbesartan/hydrochlorothiazide formulations. The tablet was orally administered with 200 ml water under fasting conditions. There were 2 dosing periods, separated by a washout period of ≥ 7days.

Blood samples were collected at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 12, 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.

Results
All subjects completed the study. No major protocol deviations were reported.

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

Treatment N = 24	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	20304 ± 6488	21286 ± 6596	3213 ± 895	2.00 (1.00-4.00)	13.23 ± 5.52
Reference	20567 ± 7097	21505 ± 7097	3526 ± 1436	1.50 (067-4.00)	11.87 ± 5.20

***Ratio (90% CI)**	1.00 (0.92 - 1.08)	1.00 (0.92 - 1.08)	0.94 (0.84 - 1.06)	---	---
****CV (%)**	16	16	24	---	---

$AUC_{0-\infty}$ 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*
*** not provided by the MAH, calculated by the assessor*

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

Treatment N = 24	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	426 ± 118	446 ± 112	79.8 ± 29.5	1.67 (1.00-3.00)	9.09 ± 2.06
Reference	438 ± 130	461 ± 128	84.6 ± 34.8	1.67 (1.00-3.00)	8.71 ± 1.33
***Ratio (90% CI)**	0.98 (0.90-1.06)	0.97 (0.91-1.04)	0.95 (0.84 -1.08)	---	---
****CV (%)**	15	13	25	---	---

$AUC_{0-\infty}$ 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*
*** not provided by the MAH, calculated by the assessor*

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 Dazirok 300/12.5 mg tablets and 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.

Bioequivalence study with 300/25 mg strength
An open label, randomised, two-treatment, two-sequence, two period, crossover, single-dose, comparative oral bioequivalence study was carried out under fasting conditions in 30 healthy (18 male and 12 female) volunteers, aged 18-33 years. Each subject received a single dose (300 mg irbesartan, 25 mg hydrochlorothiazide) of one of the 2 irbesartan/hydrochlorothiazide formulations. The tablet was orally administered with 250 ml water after a 10 hour fasting period. There were 2 dosing periods, separated by a washout period of ≥ 7days.

Blood samples were collected at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 12, 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.

Results
All subjects completed the study. No major protocol deviations were reported.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of irbesartan under fasted conditions.

Treatment N = 30	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	20966 ± 8861	22284 ± 9653	3384 ±1402	1.5 (0.67-5)	15.9 ± 6.2
Reference	20854 ± 8584	22192 ± 8916	3485 ± 1425	1.33 (0.67-5)	15.9 ± 7.3
***Ratio (90% CI)**	1.00 (0.94-1.05)	1.00 (0.95-1.06)	1.03 (0.95-1.13)	---	---
CV (%)	12.6	12	20	---	---

$AUC_{0-\infty}$ 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 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of hydrochlorothiazide under fasted conditions.

Treatment N = 30	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1102 ± 243	1124 ± 245	169 ± 45	1.7 (0.67-4)	9.6 ± 1.3
Reference	1036 ± 196	1060 ± 197	162 ± 44	1.7 (1-4)	10.5 ± 1.6
***Ratio (90% CI)**	0.95 (0.91-0.99)	0.95 (0.91-0.99)	0.97 (0.90-1.04)	---	---
CV (%)	9.3	9	16.9	---	---

$AUC_{0-\infty}$ 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 Dazirok 300/25 mg tablets and CoAprovel 300/25 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.

Extrapolation of results
As the 150/12.5mg tablets are dose proportional with the 300/25 mg tablets and the conditions for a biowaiver were, met a biowaiver can be granted for this strength.

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 combination of irbesartan and hydrochloride was first approved in 1998, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of irbesartan and hydrochlorotiazide can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
Sections 4 and 5 of the final SPC are identical to the last approved version of the SPC of the reference product CoAprovel, with the exception of the text in section 4.6. In section 4.6, the text established by the PhVWP concerning the use of Irbesartan and hydrochlorothizide during pregnancy is included, although this subsection regarding hydrochlorothizide has not yet been updated in the SPC of the innovator CoAprovel.
The PhVWP has not yet established a text concerning the use of Irbesartan and hydrochlorothiazide during lactation, this is currently still in discussion. The text included in the last approved version of the SPC from the reference product CoAprovel is included in the SPC until a final decision has been made in the PhVWP. The MAH has committed to submit a variation as soon as a final decision is made in the PhvWP to change the subsection in the SPC and PIL concerning the use of Irbesartan and hydrochlorothizide during lactation.

Readability test
The MAH stated that the proposed PIL enclosed in the dossier is the same as authorised on 15 October 1998 for the reference product CoAprovel. The submitted user test was performed with a PIL similar to the CoAprovel but not identical. This is sufficient, instead of performing an user test with the PIL authorised for the reference product CoAprovel.

The MAH submitted a readability test for the products irbesartan/hydrochlorothiazide cinfa 150 mg/12.5 mg tablets. The report of the user test is dated 31 October 2008 and is submitted in Spanish and in English. The language used during the test was Spanish.
The composition of the subject population is acceptable as far as age, gender and education are concerned. The characteristics of the participants is included on page 7 and 8 of the readability report. The full test consists of a preliminary test (pilot test) involving 3 subjects, the aim of which is to detect package leaflets with serious defects and a final test involving 2 rounds of 10 subjects each, the aim of which is to verify understanding and use of the package leaflet.
The participants were asked 16 questions about the contents of the package leaflet and 4 more questions to obtain general information about the design and text. The questionnaire addressed all relevant key safety messages of the PIL. After the pilot test, 10 adults over the age of 18 were recruited in the first round. Next, 10 more subjects were recruited for the second round. After the two rounds of interviews, no changes were made to the package leaflet.

All the three subjects from the pilot test passed without difficulty and it was therefore possible to go on to do the Definitive Test. A summary was included of the results obtained from the test on the first 10 subjects (first testing round), the second 10 subjects (second testing round) and the final results covering all the answers from these 20 subjects. The criteria for the evaluation of the results of the 20 subjects were as follows:
- 90% of the information should be located in the Package Leaflet
- 90% of the information should be understood
- 80% of the answers should be correct

In any case, if the mean score obtained for a question is less than 3 (slight difficulty when finding the information), the relevant changes should be made to the package leaflet or questionnaire as appropriate. The overall conclusion of the test is that all the test subjects understood the information in the Package Leaflet without problems.

The results of the test indicate that the Package Leaflet is well organised and laid out, is easy to understand and is clearly written. The test shows that the Package Leaflet is readable and that subjects are able to act according to the information it contains. In view of these results, it is considered that the Package Leaflet evaluated satisfactorily complies with the Readability Test. Taking the above into account, it was concluded that there was no need to introduce any changes in relation to the Package Leaflet design.

The readability test itself and the evaluation report are of an acceptable quality. There were sufficient questions about the critical sections. The conclusions are clear, concise and clearly presented. Furthermore, the questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Dazirok 150/12.5 mg, 300/12.5 mg, and 300/25 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of CoAprovel 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg tablets. CoAproval 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 MAH has committed to submit a variation as soon as a final decision is made in the PhvWP to change the subsection in the SPC and PIL concerning the use of Irbesartan and hydrochlorothizide during lactation.

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 Dazirok 150/12.5 mg, 300/12.5 mg, and 300/25 mg tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 20 September 2010. Dazirok 150/12.5 mg, 300/12.5 mg, and 300/25 mg tablets is authorised in the Netherlands on 16 February 2011.

The PSUR submission cycle is 3 years, as the active substances are well known and have been marketed for many years throughout the EU,. The Data Lock Point for the first PSUR will be three years after the date of the finalisation and approval of the DCPs. The first PSUR should be submitted within 60 days from this DLP.

The date for the first renewal will be: 20 May 2014

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

<u>Quality - medicinal product</u>
- The MAH has committed to provide validation data from one specific manufacturing site on the first three production scaled batches of the 300/12.5 mg product using the API from a second manufacturing site of Irbesartan.
- Validation data for the parameter robustness will be performed by any external company, they are not available yet. The validation data will be provided as soon as available.
- The MAH has committed to include the blending time (as validated parameter) in the description of the manufacturing process.
- The MAH committed to include information concerning the sieve size and mixing times in the description of the manufacturing process, once sieve size and mixing times are finalized on the based of validation on production scaled batches.
- The MAH has committed to provide CoAs (Certificates of Analysis) of the first consecutive production scale batches of each tablet strength when they become available.
- The MAH has committed to perform full-scale validation on the first three batches of the drug product 150/12.5mg, 300/12.5 and 300/25mg manufactured at one specific site. The MAH is asked to provide the respective protocols for these validation processes.

<u>SPC</u>
- The MAH has committed to submit a variation as soon as a final decision is made in the PhvWP to change the subsection in the SPC and PIL concerning the use of Irbesartan and hydrochlorothizide during lactation.

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
CoA	Certificate of Analysis
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