CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Irbesartan/HCT Jubilant 150/12.5 mg, 300/12.5 mg and 300/25 mg, film-coated tablets Jubilant Pharmaceuticals N.V., Belgium

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/2755/001-003/DC
Registration number in the Netherlands: RVG 112346 - 112348

8 May 2017

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:	3 December 2013
Concerned Member States:	Decentralised procedure with DE, DK, SE and 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 (SmPC), 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/HCT Jubilant 150/12.5 mg, 300/12.5 mg and 300/25 mg, film-coated tablets from Jubilant Pharmaceuticals N.V. The date of authorisation was on 3 December 2013 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 SmPC.

Irbesartan
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 renin levels and angiotensin-II levels, and a decrease in plasma aldosterone concentration. Serum potassium levels are not significantly affected by irbesartan alone at the recommended doses in patients without risk of electrolyte imbalance. Irbesartan does not inhibit ACE (kininase-II), an enzyme which generates angiotensin-II and also degrades bradykinin into inactive metabolites. Irbesartan does not require metabolic activation for its activity.

Hydrochlorothiazide
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-agiotensin-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.

Combination
The combination of hydrochlorothiazide and irbesartan produces dose-related additive reductions in blood pressure across their therapeutic dose ranges. The addition of hydrochlorothiazide to 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. Limited clinical data suggest that patients not controlled with the 300 mg/12.5 mg combination may respond when uptitrated to 300 mg/25 mg. In patients not adequately controlled on 25 mg hydrochlorothiazide alone, the addition of irbesartan gave an added placebo-subtracted systolic/diastolic mean reduction of 11.1/7.2 mm Hg.

This decentralised procedure concerns a generic application claiming essential similarity with CoAprovel 150/12.5 mg, 300/12.5 mg and 300/25 mg, film-coated tablets (EU/1/98/086/001-003) which have been registered through a centralised procedure by Sanofi Pharma Bristol-Myers 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 one bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product CoAprovel 300/25 mg tablets registered in the EEA. 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.

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
Irbesartan is an established active substance described in the European Pharmacopoeia (Ph. Eur.*). Irbesartan is a white or almost white, crystalline powder which is practically insoluble in water, sparingly soluble in methanol and slightly soluble in methylene chloride. Irbesartan structure contains neither chiral nor asymmetric carbon atoms in its structure and hence does not exhibit isomerism.

The CEP procedure is used for the active substance irbesartan. 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 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
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification of the MAH is in line with the CEP specifications. These analytical methods were assessed by the EDQM in order to be granted a CEP. The specification is acceptable.

Stability of drug substance
Stability data on the active substance have been provided for long-term conditions (25°C/60% RH) up to 60 months for three batches, up to 48 months for three batches and up to 24 months for three batches; and at accelerated conditions (40°C/75% RH) up to 6 months for six batches. No changes or trends were observed. The proposed retest period of 4 years without special storage conditions is justified.

** 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.*

Hydrochlorothiazide

The second active substance is hydrochlorothiazide, an established active substance described in the European Pharmacopoeia. Hydrochlorothiazide is a white or almost white, crystalline powder which is very slightly soluble in water, soluble in acetone and sparingly soluble in ethanol (96%). It dissolves in dilute solutions of alkali hydroxides. Hydrochlorothiazide does not have any chiral centre; hence does not exhibit optical isomerism. The CEP procedure is used for the active substance hydrochlorothiazide.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification of the MAH is in line with the CEP specifications. These methods were assessed by the EDQM in order to be granted a CEP. The specification is acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production scaled batches.

Stability of drug substance
The retest period of 5 years is included on the CEP and has been assessed by the EDQM.

Medicinal Product

Composition
Irbesartan/HCT Jubilant 150/12.5 mg – are peach coloured, biconvex, oval shaped film-coated tablets of 13.7 mm, debossed with '450'on one side and plain on the other side.
Irbesartan/HCT Jubilant 300/12.5 mg – are peach coloured, biconvex, oval shaped film-coated tablets of 17.3 mm, debossed with '451'on one side and plain on the other side.
Irbesartan/HCT Jubilant 300/25 mg – are dark pink coloured, biconvex, oval shaped film-coated tablets of 17.3 mm, debossed with '452'on one side and plain on the other side.

The film-coated tablets are packed in a PVC/PVDC blister or an Al-Al coldform blister.

The excipients are:
Tablet core: Lactose monohydrate, microcrystalline cellulose (E460), pregelatinized starch, croscarmellose sodium, povidone and magnesium stearate (E572).
Film-coating: Lactose monohydrate, hypromellose, titanium dioxide (E171), macrogol, red and yellow ferric oxide (E172).

The composition of Irbesartan/HCT Jubilant 300/25 mg and 150/12.5 mg is quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substances is the same for both strengths.
For 300/12.5 mg film-coated tablets the following is applicable:

- The amount of active substances hydrochlorothiazide is less than 5% of the core tablet weight.
- The amount of a filler lactose is changed to account for the change in amount of active substance. The amounts of other core excipients is the same.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The MAH's objective was to obtain a formulation that would be essentially similar to CoAprovel® 150/12.5 mg, 300/12.5 mg and 300/25 mg.
The 300/25 mg strength was used for the bioequivalence trial. The biobatches of test and reference demonstrated similar dissolution profiles at pH 1.2, pH 4.5 and pH 6.8.
From a chemical-pharmaceutical point of view the waiver for the 150/12.5 and 300/12.5 mg strengths can be accepted. Comparative dissolution profiles of the 300/25 mg test product versus 300/12.5 mg and 150/12.5 mg test product and the reference products in pH 4.5 and pH 6.8 and pH 1.2 media have been provided, demonstrating similarity. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of wet granulation, mixing, tabletting and coating. The product is manufactured using conventional manufacturing techniques. Process validation has been performed on three production scaled batches from every strength. It has been demonstrated that the manufacturing process can adequately produce a product that is in line with the specifications.

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

Quality control of drug product
The product specification includes tests for description, identification of irbesartan and hydrochlorothiazide (HPLC), identification of titanium oxide and ferric oxide, water content, hardness, dimensions, dissolution, uniformity of dosage units, assay, related substances and microbiological quality. Release and shelf-life limits differ for water content, assay and related substances. Batch analytical data from the proposed production site have been provided on two full scaled batches per strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for two production scaled batches per strength stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). The batches were stored in the proposed PVC/PVDC-Al or Al-Al blister packaging. The batches packed in PVC/PVDC-Al blisters were also stored at intermediate conditions (30°C/65% RH) for 12 months. The conditions used in the stability studies are according to the ICH stability guideline. In the Al-Al blister at accelerated conditions an increase in water content and impurities was observed. No other trends were observed.
In the PVC/PVDC-Al blister out of specification results were observed at accelerated conditions after 3 months of storage. At intermediate conditions all batch results stayed within the specifications.
Based on the included stability data the proposed shelf life of 24 months was granted, when stored in a PVC/PVdC-Al blister or Al-Al blister with the storage condition: “Do not store above 25°C”.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is of milk sourced from healthy animals in the same conditions as milk collected for human consumption and the lactose is prepared without the use of other ruminant materials than calf rennet.

II.2 Non-clinical aspects

This product is a generic formulation of CoAprovel, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

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.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Irbesartan/HCT Jubilant 300/25 mg (Jubilant Pharmaceuticals N.V., Belgium) is compared with the pharmacokinetic profile of the reference product CoAprovel 300/25 mg tablets (Sanofi Pharma Bristol-Myers Squibb, France).

The choice of the reference product
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.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy subjects, aged 19 to 43 years. Each subject received a single dose (300 mg irbesartan/25 mg hydrochlorothiazide) of one of the 2 formulations. The tablet was orally administered under fasted conditions. There were 2 dosing periods, separated by a washout period of 12 days.

Blood samples were collected pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.25 1.50, 1.75, 2.00, 2.25, 2.50, 2.75 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours after administration of the products.

The design of this study is acceptable. The sampling scheme is adequate for both compounds.

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-two (32) subjects completed both periods of the study. Four subjects were considered as dropouts during the study, as the subjects refused to continue without stating reasons. The dataset for pharmacokinetic analysis comprised of 32 subjects.

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

Treatment N=32	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	23654.67 ± 9424.67	24171.41 ± 9457.12	4022.68 ± 1490.69	-	-
Reference	22672.99 ± 8223.39	23399.56 ± 8348.53	3859.56 ± 1425.95	-	-
***Ratio (90% CI)**	1.03 (0.96 – 1.12)	1.03 (0.95 – 1.11)	1.03 (0.95 – 1.11)	-	-
CV (%)	30.76	29.48	33.17	-	-

$AUC_{0-\infty}$ 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=32	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	1369.22 ± 341.71	1415.20 ± 347.12	212.29 ± 67.21	-	-
Reference	1333.20 ± 365.77	1384.01 ± 372.84	208.00 ± 53.91	-	-
***Ratio (90% CI)**	1.03 (0.97 –1.10)	1.03 (0.96 – 1.09)	1.00 (0.94 – 1.07)	-	-
CV (%)	23.44	22.85	25.67	-	-

$AUC_{0-\infty}$ 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 hydrochlorothoazide under fasted conditions, it can be concluded that Irbesartan/HCT Jubilant 300/25 mg and the CoAprovel 300/25 mg 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 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 and 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.

- A biowaiver for the other strengths (300/12.5 mg and 150/12.5 mg) has been requested. This can be accepted as all conditions of the current guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled:All strengths are manufactured by the same manufacturing process.
- Pharmacokinetics of both irbesartan and hydrochlorothiazide is linear over the therapeutic range.
- The qualitative composition of the different strengths is the same.
- The composition of irbesartan and hydrochlorothiazide 300/25 mg and 150/12.5 mg strengths are quantitatively proportional.
- For 300/12.5 mg film-coated tablets the following conditions are fulfilled:
    - the amount of hydrochlorothiazide is less than 5% of the core tablet weight.
    - the amount of a filler is changed to account for the change in amount of active substance.

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 fixed dose combination irbesartan/hydrochlorothiazide was first approved 1998, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of irbesartan and hydrochlorothiazide can be considered to be well established and no product specific

pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SmPC. 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 (RMP) is not necessary for this product. This application has been submitted before 21 July 2012, i.e. before the new pharmacovigilance legislation was in force. Therefore it is acceptable that there is no RMP.

Product information

SmPC
The SmPC is similar to the product information of the innovator CoAprovel, including warnings regarding a dual blockade of RAAS (Renin-Angiotensin-Aldosterone-System).

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. Before the actual test one pilot round with 2 participants was performed. The actual test concerned of two rounds with 10 participants.
The test consisted of 17 questions specific to irbesartan and hydrochlorothiazide and some questions specific to the format of the package leaflet. Results were measured quantitatively and qualitatively. The results showed that all participants found all questions and also correctly understood the answers. Therefore no weaknesses of the PL have been identified. The success criteria are met and the test is acceptable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Irbesartan/HCT Jubilant 150/12.5 mg, 300/12.5 mg and 300/25 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of CoAprovel 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 SmPC is consistent with that of the reference product. The SmPC, package leaflet and labelling are in the agreed templates.

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/HCT Jubilant with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 12 September 2013. Irbesartan/HCT Jubilant 150/12.5 mg, 300/12.5 mg and 300/25 mg, film-coated tablets were authorised in the Netherlands on 3 December 2013.

The date for the first renewal will be: 12 September 2018.

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

<u>Quality - medicinal product</u>

- The MAH committed to review the shelf life limits for the related substances and assay after completion of post approval stability studies of the first three commercial scale batches.
- The MAH committed to continue long-term stability studies on submission batches of each strength already placed on stability, for the duration of the proposed shelf life.
- The MAH committed to place the first three production batches of each strength on a long-term stability study for the duration of the proposed shelf life and on accelerated condition for a period of six months.

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
HCT	Hydrochlorothiazide
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
RAAS	Renin-Angiotensin-Aldosterone-System
SD	Standard Deviation
SmPC	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