CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Irbesartan/Hydrochloorthiazide STADA 150 mg/12.5 mg, 300 mg/12.5 mg, 300 mg/25 mg film-coated tablets Stada Arzneimittel AG, Germany

irbesartan / hydrochlorothiazide

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

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

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

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

EU-procedure number: NL/H/1919/001-003/DC
Registration number in the Netherlands: RVG 106611-2, 106615

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 of hydrochlorothiazide alone
Prescription status:	prescription only
Date of authorisation in NL:	5 July 2011
Concerned Member States:	Decentralised procedure with AT, BE, DE, DK, ES, FR, LU, PT, and SE
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/Hydrochlorothiazide STADA 150 mg/12.5 mg, 300 mg/12.5 mg, 300 mg/25 mg film-coated tablets, from Stada Arzneimittel AG. The date of authorisation was on 5 July 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 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.

This decentralised procedure concerns a generic application claiming essential similarity with CoAprovel 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 CoApproval 300/25 mg tablets registered in Germany. 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.

Irbesartan

General information
Irbesartan is an established active substance described in the European Pharmacopoeia (Ph. Eur.*). The active substance is practically insoluble in water. Irbesartan has five known polymorphic forms. Irbesartan is not hygroscopic and has no potential isomerism.

The Active Substance Master File (ASMF) procedure is used for the active substance by all suppliers. 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
Supplier 1 - The manufacturing process consists of 6 steps. The starting materials have been described, No class 1 solvents or metal catalysts are used in the manufacturing process. The active substance has been adequately characterized. The specifications that have been adopted for the starting material, solvents and reagents are acceptable.

Supplier 2 - The manufacturing process consists of 3 steps. No class 1 organic solvents or heavy metal catalysts are used in the manufacturing process. The starting materials have been described. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Supplier 3 - The manufacturing process consists of 5 steps. No class 1 organic solvents are used. The starting materials have been described. The catalyst used has been described. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur.* and with the respective EDMF's with an additional requirement. The specification is acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two full-scale batches for each supplier.

Stability of drug substance
Supplier 1 - Stability data on the active substance have been provided for three full-scale batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The batches were adequately stored. No changes or trends are seen from the stability data. The proposed retest period of 36 months for the drug product without additional storage requirements is justified.

Supplier 2 - Stability data on the active substance have been provided for three pilot scale batches stored at 25°C/60% RH (48 months) and 40°C/75% RH (6 months) and three full-scale batches stored at 25°C/60% RH (24 months). The batches were adequately stored. No changes are seen at both conditions. The proposed retest period of 48 months without additional storage requirements is justified.

Supplier 3 - Stability data on the active substance have been provided for three full-scale batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months) and another four full-scale batches stored at 25°C/60% RH up to 48 months. The batches were adequately stored. No changes or trends are seen under both conditions. The proposed retest period of 60 months without additional storage requirements is justified.

Hydrochlorothiazide

General information
The second active substance is hydrochlorothiazide, an established active substance described in the European Pharmacopoeia. The active substance is very slightly soluble in water. No evidence of polymorphism has been reported for hydrochlorothiazide.

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 CEP. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two full-scale batches.

Stability of drug substance
The active substance is stable for 5 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 STADA 150 mg/12.5 mg - are pink, oblong, biconvex film-coated tablet and approximately 13 mm in length.
Irbesartan/Hydrochloorthiazide STADA 300 mg/12.5 mg - are pink, oblong, biconvex film-coated tablet and approximately 16 mm in length.

Irbesartan/Hydrochloorthiazide STADA 300 mg/25 mg – are red, oblong, biconvex film-coated tablet and approximately 16 mm in length.

The excipients are:
Tablet core: lactose monohydrate, maize starch, pregelatinized, copovidone, croscarmellose sodium (E468), colloidal anhydrous silica (E551), magnesium stearate (E470b).
Film-coating: hypromellose (E464), titanium dioxide (E171), talc, macrogol 8000, iron oxide yellow (E172), iron oxide red (E172), iron oxide black (E172).

The 150/12.5mg and 300/25mg tablet cores are manufactured dose proportional. The 300/12.5mg tablet cores have exactly the same composition as the 300/25mg tablet cores except for the amount of hydrochlorothiazide only. The 150/12.5mg tablets are smaller than the other tablet strengths and the 300/12.5 and 300/25 mg tablets are of the same size and shape but are sufficiently distinguishable by a difference in colour. The film-coated tablets are packed into PVC/PVDC/Aluminium blisters.
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 study comprised the characterisation of the originator product and the performance of comparative dissolution studies. The choices of the packaging and the manufacturing process are justified. The batch used in the BE study was manufactured according to the finalized composition and manufacturing process. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for at least three pilot-scale batches per strength supplemented with smaller batches up to a total of 6 batches per strength. Batches were manufactured at both manufacturing sites. The product is manufactured using conventional manufacturing techniques. Process validation for-full scale batches will be performed post authorization.

Excipients
The excipients comply with the Ph.Eur. or in-house specifications. The specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, average mass, resistance to crushing, disintegration, identity, assay, uniformity of dosage units, dissolution, related substances and microbiological quality. Except for related substances the release and shelf-life limits are identical. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production sites have been provided on two pilot scale batches per strength for the first manufacturing site and three pilot scale batches for the second site, 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, since some excipients may tend to support microbial growth. Microbiological quality is tested according to the requirements of Ph.Eur. monograph 5.1.4 during as part of the stability studies.

Stability tests on the finished product
Stability data has been provided on three batches per strength from both manufacturing sites. At least three batches per strength were of pilot-scale. The batches were stored at 25°C/60% RH (up to 18 months), 30°C/65% RH (up to 12 months) 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. No trends or changes are observed at long-term (25°C/60% RH) and intermediate (30°C/65% RH) storage conditions. At the accelerated storage conditions (40°C/75% RH) a significant increase of a hydrochlorothiazide related impurity is observed leading to an out-of-specification after 6 months. The

proposed shelf life of 24 months and storage condition '*Store below 30°C*' is justified. The MAH has committed to perform a post-approval stability study on three production batches of the 150/12.5mg and 300/25mg strengths and one production batch of the 300/12.5 mg strength. In addition, the ongoing stability studies will be continued up to 60 months long-term according to the stability protocol. The results of the ongoing stability studies at least up to the proposed retest period of 24 months are awaited.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The milk used for the manufacture of lactose monohydrate is 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. Magnesium stearate is of vegetable origin. So, a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

This product is a generic formulation of CoAprovel tablets, 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 hyddrochlorothiazide 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

Pharmacokinetics
Irbesartan
The absolute bioavailability of irbesartan is 60 – 80%. Irbesartan exhibits linear kinetics between the 10 mg and 600 mg dosing range, and reaches steady-state within 3 days.
The bioavailability of irbesartan is not significantly affected by the coadministration of food, therefore, irbesartan can be administered without regard to the timing of meals.
Irbesartan is 90% bound to serum proteins.
Irbesartan is metabolized through glucuronide conjugation and oxidation, with irbesartan glucuronide as the major circulating metabolite (6%). Over 80% of the drug remains unchanged. The metabolites of irbesartan are pharmacologically inactive. Approximately 20% of irbesartan and its metabolites are excreted in the urine, and the remainder are excreted in the feces.

Hydrochlorothiazide
The absorption of hydrochlorothiazide is rapid, with a T_{max} of 1-2.5 hours, and is 50%-80% complete. The reported studies of food effects on hydrochlorothiazide absorption have been inconclusive.
Hydrochlorothiazide is not metabolized.
The drug is 67.9% bound to plasma proteins, and it also accumulates in red blood cells so that whole blood levels are 1.6-1.8 times those measured in plasma.
Thiazide diuretics are eliminated by the kidney, with a terminal half-life of 5-15 hours.

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 STADA 300 mg/25 mg film-coated tablets (Stada Arzneimittel AG, Germany) is compared with the pharmacokinetic profile of the reference product CoAprovel 300/25 mg tablets (Sanofi Aventis GmbH, Germany).

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.

Bioequivalence study
A single-dose, randomized, open-label, 2-way crossover, bioequivalence study was carried out under fasted conditions in 36 (27 male, 9 female) healthy volunteers, aged 18-50 years with a BMI of 19 - 28. Each subject received a single dose (300 mg irbesartan / 25 mg hydrochlorothiazide) of one of the 2 irbesartan/hydrochlorothiazide formulations. A randomization scheme was provided. The tablet was orally administered with 240 ml water after an overnight fast of 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected predose and at 0.250, 0.500, 0.750, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 12.0, 16.0, 24.0, 36.0 (± 0.5), and 48.0 (± 0.5) 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. During the study several quality assessments were preformed.

Results
Three subjects withdrew from the study: one for personal reasons, one for positive alcohol breath test and one for non compliance with respect to information. Thirty-three 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 = 33	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	20.85 ± 9.33	23.08 ± 12.15	3.00 ± 0.99	1.75 0.5 – 5.0	14.6 ± 5.9
Reference	19.47 ± 8.19	21.69 ± 10.72	3.19 ± 1.21	1.25 0.5 – 5.0	13.8 ± 6.6
***Ratio (90% CI)**	1.06 0.99 – 1.14	1.06 0.98 – 1.14	0.94 0.85 – 1.04	---	---
CV (%)	17	18	23	---	---

$AUC_{0-\infty}$ 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 = 33	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	932 ± 250	957 ± 255	139 ± 46	2.0 0.75 – 4.0	9.8 ± 1.1
Reference	940 ± 306	966 ± 307	150 ± 58	1.75 1.0 – 3.5	10.1 ± 2.1
***Ratio (90% CI)**	1.01 0.94 – 1.09	1.01 0.94 – 1.08	0.96 0.85 – 1.08	---	---
CV (%)	19	17	30	---	---

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

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of irbesartan and hydrochlorothiazide under fasted conditions, it can be concluded that Irbesartan/Hydrochloorthiazide STADA 300 mg/25 mg film-coated tablets and the 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
According to the CPMP guideline "Note for guidance on the investigation of bioavailability and bioequivalence" (CPMP/EWP/QWP/1401/98), a bioequivalence study investigating only one tablet strength may be acceptable if all of the following conditions are fulfilled:

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

All these conditions hold for irbesartan/HTC manufactured by the MAH, therefore it would be considered that the 150/12.5 mg will also be bioequivalent to their respective counterparts. A comprehensive justification was submitted by applicant in the Clinical Overview.
With respect to the 300/12.5 mg formulation, this formulation only differs from the 300/25 mg with respect to the amount hydrochlorothiazide. As this is less than 5% of the total weight extrapolation from the 300/25 to the 300/12.5 is considered acceptable.

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 in 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 postauthorisation 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 is not necessary for this product.

Product information

SmPC
Sections 4 and 5 of the final SmPC are identical to the text of the authorised reference product CoAprovel, with exception of the text on pregnancy and lactation in section 4.6:
Regarding pregnancy: The PhVWP has established a text concerning the use of Irbesartan and hydrochlorothiazide during pregnancy and this text is now included in section 4.6 of the SmPC, although the SmPC of the reference product CoAprovel concerning the use of Irbesartan and hydrochlorothiazide during pregnancy has not yet been updated.
Regarding lactation: The PhVWP has not yet established a text concerning the use of Irbesartan and hydrochlorothiazide during lactation, this is currently still in discussion. During the DCP, it is agreed that the text of the last approved version of the SmPC from the reference product CoAprovel is included in the SmPC until a final decision has been made in the PhVWP.
Furthermore, the MAH submitted a commitment that they will submit a variation, as soon as a final decision is made and a final text proposal is agreed in the PhVWP, to change the SmPC and PIL section concerning the use of Irbesartan and hydrochlorothiazide during lactation accordingly.

Section 4.4 with regard to Anti-doping tests
The information concerning the Anti-doping test is included as blue box text in some Member states, both in section 4.4 of the SmPC, as well as in the PL.

Readability test
No user testing with regard to the content of the PL has been carried out. This is acceptable because the PL enclosed in the dossier is identical to the PL of the authorised reference product CoAprovel which is authorised via centralised procedure in the European Community with the exception the product-specific information in sections 5 and 6.

The lay-out of the PL has been assessed as the design and layout of the information in the PIL is crucial to the way in which patients access the key messages for safe use. The "*house style*" from STADA Arzneimittel AG was assessed with regard to the design, layout and style of writing. The following important aspects were considered:

- Font text size and type
- Heading structure using shaded boxes
- Text alignment
- White space around headings and between lines
- PL length
- Finding results
- Subjective rating of the layout usability given by test participants

The submitted documentation from the testing facility is acceptable and the statement that the lay-out used by STADA supports patients in finding all key safety messages in the PL is supported.

The MAH confirmed that the assessed lay-out from STADA Arzneimittel AG will be used as lay-out of the PIL for Irbesartan/Hydrochloorthiazide STADA.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Irbesartan/Hydrochloorthiazide STADA 150 mg/12.5 mg, 300 mg/12.5 mg, 300 mg/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, package leaflet and labelling are in the agreed templates. The MAH has committed to submit a variation to change the SmPC and PIL section concerning the use of Irbesartan and hydrochlorothiazide during lactation as soon as a final decision is made and a final text proposal is agreed in the PhVWP. Braille conditions are met by the MAH.

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 STADA 150 mg/12.5 mg, 300 mg/12.5 mg, 300 mg/25 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 21 December 2010. Irbesartan/Hydrochloorthiazide STADA 150 mg/12.5 mg, 300 mg/12.5 mg, 300 mg/25 mg film-coated tablets are authorised in the Netherlands on 5 July 2011.

The PSUR submission scheme is 3 years upon approval of this DCP. The Data Lock point for the first PSUR is 21 December 2013 and should be submitted within 60 days after the DLP.

The date for the first renewal will be: 21 August 2014.

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

<u>Quality - medicinal product</u>
- The MAH has committed to perform a post-approval stability study on three production batches of the 150/12.5mg and 300/25mg strengths and one production batch of the 300/12.5 mg strength.
- The ongoing stability studies will be continued up to 60 months long-term according to the stability protocol. The results of the ongoing stability studies at least up to the proposed retest period of 24 months are awaited as soon as available.

<u>SmPC</u>
- The MAH has committed to submit a variation, as soon as a final decision is made and a final text proposal is agreed in the PhVWP, to change the SmPC and PIL section concerning the use of Irbesartan and hydrochlorothiazide during lactation accordingly.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
BMI	Body Mass Index
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
PhVWP	Pharmacovigilance Working Party
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
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
Change in the name of the medicinal product.	NL/H/1919/ 001-003/IB/ 001	IB	11-4-2011	20-6-2011	Approval	N