CBG MEB

Public Assessment Report

Scientific discussion

Irbecell HCT 150/12.5 mg, film-coated tablets
Irbecell HCT 300/12.5 mg, film-coated tablets
Irbecell HCT 300/25 mg, film-coated tablets

(irbesartan/hydrochlorothiazide)

NL License RVG: 113266, 113267, 113268

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This module reflects the scientific discussion for the approval of Irbecell HCT 150/12.5 mg; 300/12.5 mg; 300/25 mg, film-coated tablets. The marketing authorisations were granted on 13 February 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Irbecell HCT 150/12.5 mg; 300/12.5 mg; 300/25 mg, film-coated tablets, from Medcell Pharma B.V.

The product is indicated for the treatment of essential hypertension in adults 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.

This national procedure concerns a generic application claiming essential similarity with the innovator products CoAprovel 150/12.5 mg; 300/12.5 mg; 300/25 mg, film-coated tablets, which have been registered via the centralised procedure by Sanofi Pharma Bristol-Meyers Squibb SNC since 1998 (original product).

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Irbecell HCT 150/12.5 mg is a pink, biconvex, oval shaped film-coated tablet measuring 6.5 x 12.7 mm, debossed with 'H' on one side and 'I' on the other side, and contains as active substances 150 mg irbesartan and 12.5 mg hydrochlorothiazide.
Irbecell HCT 300/12.5 mg is a pink, biconvex, oval shaped film-coated tablet measuring 8.2 x 16.0 mm, debossed with 'H' on one side and 'I' on the other side, and contains as active substances 300 mg irbesartan and 12.5 mg hydrochlorothiazide.
Irbecell HCT 300/25 mg is a pink, biconvex, oval shaped film-coated tablet measuring 8.2 x 16.0 mm, debossed with 'H' on one side and 'I' on the other side, and contains as active substances 300 mg irbesartan and 25 mg hydrochlorothiazide.

The film-coated tablets are packed in Al-PVC/PVDC or Al-PVC/Aclar/PVDC/PCV blister packs.

The excipients are:
Tablet core: mannitol (E421), povidone (K29-32 or equivalent), microcrystalline cellulose, croscarmellose sodium, silica colloidal anhydrous, magnesium stearate
Film-coating: polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc, iron oxide yellow (E172), iron oxide red (E172). For Irbecell HCT 300/12.5 mg and 300/25 mg only: iron oxide black (E172)

The 150/12.5 mg and 300/25 mg strengths are dose proportional. The 300/12.5mg and 300/25mg have the same composition, mannitol is used for compensation of the active ingredient of the lower strength.

II.2 Drug Substances

Irbesartan

The active substance irbesartan is an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white to off-white crystalline powder, which is slightly soluble in ethanol (96%), chloroform, methylene chloride and practically insoluble in water. Further, irbesartan is freely soluble in dilute alkaline solution. The substance is not hygroscopic, but does exhibit polymorphism, where Form A is the anticipated form.

The Active Substance Master File (ASMF) procedure is used for one manufacturer of the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing

authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA 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 the second supplier of the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the 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
For the DMF holder, sufficient data on the manufacturing process have been provided.
For the other manufacturer a CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. monograph for irbesartan with appropriate additional requirements. The specification is acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two batches manufactured by the DMF holder and five batches manufactured by the CEP holder.

Stability of drug substance
For the first manufacturer stability data on the active substance have been provided for a total of 18 batches of both pilot and commercial scale. The batches were stored at 25 ± 2°C/60 ± 5% RH (for up to 3, 6,18, 24, or 48 months) and at 40 ± 2°C/75 ± 5% RH (for up to 3 or 6 months). From the provided data no significant changes are seen at both accelerated and long-term conditions. Based on these data, the proposed retest period of 36 months is acceptable.
As stated on the CEP from the second manufacturer, the shelf life is 3 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Hydrochlorothiazide

The active substance hydrochlorothiazide is also an established active substance described in the Ph. Eur. Hydrochlorothiazide is very slightly soluble in water, soluble in acetone, sparingly soluble in ethanol (96 per cent) and it dissolves in dilute solutions of alkali hydroxides. Two different manufacturers using CEPs are used.

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

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data have been provided for one batch.

Stability of drug substance
For both manufacturers, the active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEPs and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.
The development of the product has been described, the choice of excipients is justified and their functions explained. During the development of the product, a number of studies were performed, in which parameters such as flow properties, prevention of filming, how compact the formulation was, and stability were tested, leading to the final composition. This final composition was used for manufacturing of the biobatches.

The composition of the tablets used in the bioequivalence studies is identical to the proposed commercial composition. The bioequivalence studies were performed with the 300/25 and 300/12.5 mg tablets. For the 150/12.5 mg strength a biowaiver of strength is applied, as dose proportionality with the 300/25 mg strength is claimed. This biowaiver of strength is adequately supported by a comparison of dissolution characteristics between a 300/25 mg batch and the 150/12.5 mg batch at three pH values..

Manufacturing process
The manufacturing process of the proposed product involves blending and sieving, mixing, wet granulation, screening, drying, sieving, mixing, tableting and coating. The manufacturing of the drug product is considered a standard process. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three to five batches of each strength for each of the two proposed manufacturing sites in accordance with the relevant European guidelines.

Control of excipients
With the exception of the Opadry colouring agents, all excipients comply with the Ph.Eur. For the Opadry colouring agents, all the individual components comply with the Ph.Eur. or USP (iron oxide). The applicant states that the Opadry colouring agents are controlled according to an in-house specification, specifications as well as a brief description of the analytical methods used have been provided. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for tablet description, identification (of irbesartan, HCT, titanium dioxide and iron oxide), uniformity of dosage units, disintegration, dissolution, assay, related substances, loss on drying and microbiology. The release and shelf-life requirements are identical, with the exception of loss on drying, uniformity of dosage units, which is not tested at shelf life, and for some of the impurities. The proposed specification is considered acceptable. The analytical methods have been adequately described and validated, stability indicating nature of the methods has been shown.
Sufficient batch analytical data have been provided for pilot and commercial scale batches of all strengths manufactured at the two manufacturing sites, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product have been provided for 6 to 9 batches per strength stored at 25°C/60% RH (up to 36 months), 30°/75% RH (up to 24 months) and 40°C/75% RH (up to 6 months). The conditions used in the stability studies are according to the ICH stability guideline. Photostability is sufficiently demonstrated. Based on the data submitted, a shelf life of 2 years was granted. The product packed in Al/PVC/PVDC (60 g/m2) must be stored below 25ºC. No special storage conditions are necessary for the product packed in PVC/Aclar/PVDC/PVC and Al/Al/PVDC (180 g/m2) blisters.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Irbecell HCT film-coated tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- Three commercial scale validation batches of the drug substance are subjected to accelerated and long-term studies. Thereafter, one annual lot is placed on long-term studies. Accelerated stability studies are conducted at 40±2ºC/75±5% RH for 6 months. Long term stability studies are conducted at 25±5ºC/60±5% RH for a maximum of 5 years. The stability studies are conducted on the drug substance packaged in a container closure system that is the same as or simulates the packaging proposed for storage and distribution.
- Stability studies on the drug product will be continued for all tested batches in the packaging material indicated. It is confirmed that the first two commercial batches of strengths 150/12.5 mg and 300/25 mg

will be added to the stability program. For the strength 300/12.5 mg the first three commercial scale batches will be placed on stability.
Thereafter, a minimum of one batch annually will be placed on stability in accordance with GMP.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Irbecell HCT film-coated tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of CoAprovel which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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 MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

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 MEB agrees that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profiles of the test products Irbecell HCT 300/12.5 and 300/25 mg, film-coated tablets (Medcell Pharma B.V., the Netherlands) are compared with the pharmacokinetic profiles of the reference product CoAprovel 300/12.5 and 300/25 mg (Sanofi Pharma Bristol-Myers Squibb SNC, United Kingdom).

The choice of the reference product in the bioequivalence studies is justified as CoAprovel is registered through the centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
The MAH applied for a biowaiver for the 150/12.5 mg strength, as it is dose proportional with the 300/25 mg strength. A biowaiver was granted, as the following conditions are met:

- the products are manufactured by the same manufacturer and process
- the qualitative composition of the different strengths is the same
- the ratio between the amounts of active substance and excipients is the same
- the dissolution profiles are similar under identical conditions for the additional strengths.
- From literature it can be concluded that irbesartan exhibits linear and dose proportional pharmacokinetics over the dose range of 10 mg to 600 mg.

Bioequivalence studies

Study 1: 300/25 mg strength

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 30 healthy male subjects, aged 19-42 years. Each subject received a single dose (300/25 mg) of one of the 2 irbesartan/hydrochlorothiazide formulations. The tablet was orally administered with 240 ml of water after an overnight fast. Fasting was maintained until four hours post dose. There were 2 dosing periods, separated by a washout period of 7 days.
Blood samples, to be analysed for irbesartan and hydrochlorothiazide were drawn pre-dose and at 0.17, 0.33, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 12, 24, 36 and 48 hours post dose.

The design of the study is acceptable.

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 the active substances. 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.

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
Two subjects were withdrawn from the study, one because he did not report for period 2 and one because he tested positive for a urine drug test before period 2. Twenty-eight subjects were eligible for pharmacokinetic analysis.

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

Treatment N=28	**AUC_{0-t}** µg/ml/h	**$AUC_{0-\infty}$** µg /ml/h	**C_{max}** µg /ml	**t_{max}** h
Test	17.3 ± 5.5	18.6 ± 5.6	4.1 ± 1.7	1.33 (0.75-4.5)
Reference	19.3 ± 8.9	20.3 ± 8.8	3.7 ± 2.1	1.83 (0.5-4.5)
***Ratio (90% CI)**	0.92 (0.87-0.97)	0.94 (0.89-0.99)	1.12 (1.05-1.18)	--

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**ln-transformed values*

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

Treatment N=28	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng /ml/h	**C_{max}** ng /ml	**t_{max}** h
Test	966 ± 172	997 ± 176	136 ± 44	2.17 (1.0-4.0)
Reference	1005 ± 227	1038 ± 235	136 ± 37	2.17 (1.0-4.5)
***Ratio (90% CI)**	0.97 (0.92-1.02)	0.97 (0.92-1.02)	1.00 (0.93-1.08)	--

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**ln-transformed values*

Study 2: 300/12.5 mg strength

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 30 healthy male subjects, aged 18-55 years. Each subject received a single dose (300/12.5 mg) of one of the 2 irbesartan/hydrochlorothiazide formulations. The tablet was orally administered with 240 ml of water after a 10 hour fast. Fasted was maintained until four hours post dose. There were 2 dosing periods, separated by a washout period of 10 days.
Blood samples, to be analysed for irbesartan and hydrochlorothiazide were drawn pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, 36 and 48 hours post dose.

The design of the study under fasted conditions is acceptable.

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
One subjects was withdrawn from the study because he did not report for period 2. Twenty-nine subjects were eligible for pharmacokinetic analysis.

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

Treatment N=29	AUC_{0-t} µg/ml/h	$AUC_{0-\infty}$ µg /ml/h	C_{max} µg /ml	t_{max} h
Test	19.8 ± 6.1	21.5 ± 7.2	3.9 ± 1.0	2.0 (0.5-4.5)
Reference	19.3 ± 5.9	20.8 ± 6.6	3.7 ± 0.9	1.0 (0.5-4.5)
***Ratio (90% CI)**	1.03 (0.95-1.12)	1.03 (0.96-1.12)	1.06 (1.00-1.14)	--

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**ln-transformed values*

Table 4. Pharmacokinetic parameters for hydrochlorothiazide (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment N=29	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng /ml/h	C_{max} ng /ml	t_{max} h
Test	547 ± 130	566 ± 131	75 ± 17	2.0 (1.0-5.0)
Reference	521 ± 112	551 ± 114	72 ± 17	2.0 (1.0-5.0)
***Ratio (90% CI)**	1.02 (0.96-1.09)	1.02 (0.96-1.09)	1.04 (0.96-1.13)	--

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**ln-transformed values*

Conclusion on bioequivalence studies:

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the acceptance range of 0.80 – 1.25 in for both irbesartan and hydrochlorothiazide in both studied strengths. Based on the submitted bioequivalence studies Irbecell HCT film-coated tablets are considered bioequivalent with CoAprovel.

The MEB has been assured that the bioequivalence studies have 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).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Irbecell HCT, film-coated tablets.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Hyperkalaemia - Hypotension - Foetotoxicity
Important potential risks	- Elevation of liver function values - Renal impairment - Hypersensitivity reactions including angioedema and serum sickness - Decrease in haemoglobin and/or haematocrit
Missing information	- Exposure during breastfeeding - Exposure in paediatric patients

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product CoAprovel. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English. The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Irbecell HCT 150/12.5 mg; 300/12.5 mg; 300/25 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of CoAprovel 150/12.5 mg; 300/12.5 mg; 300/25 mg, film-coated

tablets. Co-Aprovel 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 Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Irbecell HCT, film-coated tablets with the reference product, and has therefore granted a marketing authorisation. Irbecell HCT, film-coated tablets was authorised in the Netherlands on 13 February 2014.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Replacement of the manufacturer responsible for batch release	IA variation	26 June 2014	11 August 2014	Non-approval	N
Update CEP	IA variation	21 August 2014	25 August 2014	Approval	N
Replacement of the manufacturer responsible for batch release (resubmission)	IA variation	18 March 2015	14 April 2015	Approval	N