CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Irbecell 75 mg, 150 mg and 300 mg, film-coated tablets
Medcell Pharma B.V., the Netherlands

irbesartan

Registration number in the Netherlands: RVG 113082-113084

8 April 2014

Pharmacotherapeutic group:	angiotensin II antagonists, plain
ATC code:	C09CA04
Route of administration:	oral
Therapeutic indication:	essential hypertension; renal disease in patients with hypertension and type 2 diabetes mellitus
Prescription status:	prescription only
Date of authorisation in NL:	3 September 2013
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 Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Irbecell 75 mg, 150 mg and 300 mg, film-coated tablets from Medcell Pharma B.V. The date of authorisation was on 3 September 2013 in the Netherlands.

The product is indicated for:
- treatment of essential hypertension in adults.
- treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive medicinal product regimen.

A comprehensive description of the indications and posology is given in the SPC.

Irbesartan is a potent, orally active, selective angiotensin II receptor (type AT1) antagonist. It is expected to block all the 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. 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.

This national procedure concerns a generic application claiming essential similarity with the innovator products Aprovel 75 mg, 150 mg and 300 mg tablets which have been registered through centralised procedure EU/1/97/049/001-003 by Sanofi Pharma Bristol-Myers Squibb Pharma EEIG since 1997.
Further information can be found in the EPAR of Aprovel (http://www.ema.europa.eu/htms/human/epar/).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Aprovel 300 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 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 a generic application.

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 substance is irbesartan, 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.

** 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.*

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 supplier 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.

Medicinal Product

Composition
Irbecell 75 mg is a white, elliptical, biconvex, film-coated tablet, marked 'I' on one side and '75' on the other side.
Irbecell 150 mg is a white, elliptical, biconvex, film-coated tablet, marked 'I' on one side and '150' on the other side.
Irbecell 300 mg is a white, elliptical, biconvex, film-coated tablet, marked 'I' on one side and '300' on the other side.

The film-coated tablets are packed in PVC/PVdC/Al blisters or HDPE bottles with a LDPE cap.

The excipients are:
Core – croscarmellose sodium, microcrystalline cellulose, hypromellose and mannitol, magnesium stearate, colloidal anhydrous silica
Film-coating - hydroxypropyl cellulose, hypromellose, macrogol 6000, titanium dioxide.

The three strengths are dose proportional.

Pharmaceutical development
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, leading to the final composition. This final composition was used for manufacturing of the biobatch. After production of the first commercial-scale Irbecell tablets the MAH considered slight changes to the composition of the coating solution necessary. The new coating is acceptable based on the provided stability data.
The MAH has performed a bioequivalence study with the 300 mg product, and applied for a biowaiver for the remaining two strengths. Sufficient comparative dissolution data were provided to support the biowaiver from a quality point of view. Hence, the pharmaceutical development of the product has been adequately described.

Manufacturing process
The manufacturing process of the proposed product involves mixing, wet granulation, screening, drying, blending and tableting. The manufacturing of the drug product is considered a standard process. The MAH has provided sufficient details concerning the description of the process, holding times and the minor changes made on the manufacturing process during development.
The manufacturing process has been adequately validated. Six batches of the common blend and three batches of each strength were subjected to validation, showing adequate results.

Control of excipients
All the excipients comply with the Ph.Eur., except for Opadry white, for which an in-house quality standard is applied. The MAH has provided specifications and a description of the analytical procedures used for Opadry white, these specifications are acceptable. All individual components of the Opadry white comply with the Ph.Eur.

Quality control of drug product
The product specification includes tests for tablet description, identification, uniformity of dosage units, average weight, resistance to crushing, disintegration, dissolution, assay, related substances and microbiology. The release and shelf-life requirements are identical, with the exception of uniformity of dosage units, which is not tested at shelf life, and the limit for assay.
The analytical methods have been adequately described and validated. Sufficient batch analytical data have been provided for pilot- and commercial-scale batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided for 30 batches on pilot- and commercial-scale stored at 25°C/60% RH (up to 36 months), 30°/65% RH/or 30°C/75% RH (up to 3/12/18 or 24 months) and 40°C/75% RH (up to 3 or 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 and HDPE bottles.
From the available nine months data for the batches with new coating, the stability profile appears to be similar to the batches with the old coating. Additional stability studies are initiated for the product manufactured at a second site (with the new coating). The six months data show similar results. The finished product has been demonstrated to be photostable. Overall, the proposed storage time of 24 months is considered acceptable. No special storage conditions are required.

Stability data has been provided demonstrating that the product remains stable for 6 months following first opening of the bottle, when stored at 25°C/60% RH. Considering the results, no in-use shelf life is necessary.

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.2 Non-clinical aspects

This product is a generic formulation of Aprovel, 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 Board 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 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 is a well-known active substance 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 Board 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 Irbecell 300 mg (Medcell Pharma B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Aprovel 300 mg film-coated tablets (Sanofi Pharma Bristol-Myers Squibb SNC, from the German market).

The choice of the reference product
The reference product is acceptable, as Aprovel is registered through the centralised procedure. The innovator product obtained from the German market is thus considered identical to the product available in the Netherlands.

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 18-38 years. Each subject received a single dose (300 mg) of one of the 2 irbesartan formulations. There were 2 dosing periods, separated by a washout period of 11 days.

Blood samples were collected 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, 5, 6, 8, 12, 24, 36, 48 and 72 hours after administration of the products.

The Board considers this an acceptable design with an adequate wash-out, decent sampling period and sampling scheme.

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 withdrawn: one due to an adverse event (skin rash) between periods and another subject as he tested positive for benzodiazepine during screening for period 2. A total of 28 subjects completed the study and were included in pharmacokinetic and statistical analysis.

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

Treatment N=28	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	16.0 ± 4.7	17.2 ± 4.9	3.5 ± 0.9	1.67 (0.5-4.0)	--
Reference	16.2 ± 7.1	17.1 ± 7.3	3.8 ± 1.4	1.33 (0.5-5.0)	--
***Ratio (90% CI)**	0.99 (0.92-1.07)	1.00 (0.92-1.08)	1.07 (0.98-1.16)	--	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$ 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 under fasted conditions, it can be concluded that Irbecell 300 mg and Aprovel 300 mg film-coated 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 may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of irbesartan. 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.

Extrapolation to other strengths
In accordance with the CPMP guidance, the results of the bioequivalance study can be extrapolated to the 75 mg and 150 mg strength, as 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 is similar under identical conditions for the additional strengths and the strength of the biobatch.

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
As required based on current pharmacovigilance legislation, the MAH provided a Risk Management Plan. In line with RMPs of other Angiotensin II receptor antagonists, the following risks have been included: RMP as a minimum requirement:

Important identified risks	Hyperkalaemia Hypotension Foetotoxicity
Important potential risks	Elevation of liver function values Renal impairment Hypersensitivity reactions incl. angioedema and serum sickness Decrease in haemoglobin and/or hematocrit
Important missing information	Exposure in paediatric patients Exposure during breast feeding

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.

Product information

SmPC
The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product Aprovel.

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. The test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. All of the test questions were dealt with successfully with no difficulty understanding. For 97.3% of the test questions, the subjects located the information very easily or easily. The success criteria were met in both rounds. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Irbecell 75 mg, 150 mg and 300 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Aprovel 75 mg, 150 mg and 300 mg tablets. 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 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 and are in agreement with other irbesartan containing products.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. Irbecell 75 mg, 150 mg and 300 mg, film-coated tablets was authorised in the Netherlands on 3 September 2013.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
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