CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Irbesartan Aurobindo 150 mg and 300 mg, tablets
Aurobindo Pharma B.V., the Netherlands

irbesartan

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/2610/001-002/MR
Registration number in the Netherlands: RVG 106371-106372

17 September 2012

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 first authorisation in NL:	6 December 2010
Concerned Member States:	Mutual recognition procedure with IT
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Irbesartan Aurobindo 150 mg and 300 mg, tablets from Aurobindo Pharma B.V. The date of authorisation was on 6 December 2010 in the Netherlands.

The product is indicated for:
- treatment of essential hypertension in adults.
- treatment of renal disease in adult 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 mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Aprovel 150 mg and 300 mg tablets which have been registered through centralised procedure EU/1/97/049/001-003 by 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.

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 or almost white crystalline powder, which is practically insoluble in water, sparingly soluble in methanol and slightly soluble in methylene chloride. Two crystalline polymorphic forms are known. Form A is used. No chiral centres are present in the molecule.

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 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 is in line with the Ph.Eur. monograph for irbesartan, with additional requirements for residual solvents and particle size. The specification is acceptable in view of the Ph.Eur. monograph for irbesartan and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three pilot-scale batches.

Stability of drug substance
The active substance is stable for 24 months when stored under the stated conditions. 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 Aurobindo 150 mg is a white to off-white, biconvex oval shaped uncoated tablet debossed with 'H 29' on one side and plain on other side.
Irbesartan Aurobindo 300 mg is a white to off-white, biconvex oval shaped uncoated tablet debossed with 'H 30' on one side and plain on other side.

The tablets are packed in PVC/PVdC-Aluminium blisters and white opaque HDPE bottles.

The excipients are: microcrystalline cellulose (E460), calcium hydrogen phosphate dihydrate, sodium starch glycolate (Type A), hypromellose (E464), polysorbate 80 (E433), talc (E553b), silica colloidal anhydrous (E551), sodium stearyl fumarate.

The tablets are fully dose proportional.

Pharmaceutical development
The development of the product has been described and the choice of excipients is justified. Their functions have been explained. The manufacturing process was developed as wet granulation due to the poor flow properties, fluffy nature of the drug substance and low bulk density. As the substance has poor aqueous solubility, a surfactant (polysorbate 80) is used. The choice of formulation and the different steps of the manufacturing process have been adequately discussed. The choice of packaging material has not been justified, but the type and material of the container closure systems are deemed acceptable.
The bioequivalence study has been performed with the 300 mg strength only. All requirements for the biowaiver of the 150 mg strength have been fulfilled. The proposed drug product can be considered on quality grounds to be essentially similar to the innovator product. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The tablets are manufactured by sifting and dry mixing. The binder solution is added, the wet mass is milled, dried and sifted. The granules retained are again milled and blended, followed by lubrication, compression into tablets an packing. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two pilot-scale batches of each strength. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with their respective Ph.Eur. monographs. For some excipients, additional tests on functional characteristics have been included. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification, average mass, dissolution, uniformity of dosage units by mass variation, related substances, assay, water content, thickness and microbial contamination. Wider shelf-life limits are applied for water content only. Hardness and disintegration time are controlled as in-process controls. This is acceptable.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two pilot-scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on two pilot-scale batches of each strength stored at 25°C/60%RH for 24 months and 40°C/75%RH for 6 months. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PVdC-Alu blisters and HDPE containers. A photostability study has been performed on the 300 mg strength, demonstrating the photostability of the drug product. The in-use stability study performed for the 30's count HDPE containers demonstrates the stability of the drug product after first opening of the container. The in-use stability study of the 500's count container is ongoing.
The stability data show analytical variation for assay and water content, but no clear trends. Only for the drug product packed in blisters and stored under accelerated conditions, a clear increase in water content is observed. Based on the available stability data, a shelf-life of 2 years was granted without any specific storage conditions.

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 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 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 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 Aurobindo 300 mg (Aurobindo Pharma B.V., NL) is compared with the pharmacokinetic profile of the reference product Aprovel 300 mg tablets (Sanofi Pharma Bristol-Meyer Squibb, France).

The choice of the reference product
The reference product is acceptable, as Aprovel is registered through the centralised procedure. 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 male subjects, aged 19-42 years. Each subject received a single dose (300 mg) of one of the 2 irbesartan formulations. The tablet was orally administered with 240 ml water under fasted conditions. There were 2 dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0 and 48.0 hours after administration of the products.

Sampling times are sufficient to cover an adequate description of the pharmacokinetics. Taking into account the elimination half-life (15 h), the 8-day washout period is considered 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
There were no drop outs in this study. All 36 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=36	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	13.92 ± 6.58	14.08 ± 6.63	2.71 ± 1.10	1.75 (0.67 – 5.0)	7.6 ± 2.5
Reference	13.25 ± 5.52	13.46 ± 5.56	2.68 ± 1.08	1.5 (0.5 – 5.0)	8.5 ± 3.4

***Ratio (90% CI)**	1.04 (0.97–1.11)	1.03 (0.97–1.10)	1.01 (0.94–1.09)	--	--
CV (%)	16.9	17.0	18.3	--	--
$AUC_{0-\infty}$ 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 Irbesartan Aurobindo 300 mg and Aprovel 300 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 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 150 mg strength
The requirements for waiving bioequivalence studies mentioned in the guideline are fulfilled. This means that:
- 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 strength 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
Irbesartan was first approved in 1997, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of irbesartan 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 SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

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

Readability test
The package leaflet has not been evaluated via a user consultation study. The MAH submitted a bridging statement for not submitting the results of a readability test. Regarding the content of the leaflet, it is stated that the package leaflet of the product applied for has the same key messages for safe use as the

package leaflet of Losartan potassium Aurobindo, which package leaflet has successfully been user tested. Furthermore, the text in the package leaflet is in line with the package leaflet of the innovator product Aprovel.

With regard to the design and layout, the MAH stated that the layout, design, complexity of the message and the language used in the package leaflet applied for are similar to the leaflet of Losartan potassium Aurobindo. It is therefore claimed that the readability test result of Losartan potassium Aurobindo can be judged as relevant for the leaflet of Irbesartan Aurobindo.

The member states agree with the reasoning of the MAH and with the submitted bridging statement, concluding that it is not necessary to perform a separate user test on the leaflet of Irbesartan Aurobindo.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Irbesartan Aurobindo 150 mg and 300 mg, tablets have a proven chemical-pharmaceutical quality and are generic forms of Aprovel 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 SPC, 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. Irbesartan Aurobindo 150 mg and 300 mg, tablets were authorised in the Netherlands on 6 December 2010.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member state mutually recognised the Dutch evaluation for the marketing authorisation The CMS, on the basis of the data submitted, considered that essential similarity has been demonstrated for Irbesartan Aurobindo 150 mg and 300 mg with the reference product, and has therefore granted a marketing authorisation. The mutual recognition procedure was finished on 24 June 2012.

The date for the first renewal will be: 6 November 2014.

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

Quality - medicinal product

- The MAH committed to conduct validation on the first three commercial- and full-scale batches of each strength.
- The MAH committed to continue the long-term studies, perform long-term and accelerated stability studies on the first production batch and the first three full production-scale batches of each strength and to place a minimum of one batch on stability studies annually.

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
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached