CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Irbesartan Urquima 75 mg, 150 mg and 300 mg film-coated tablets URQUIMA S.A., Spain

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/1116/001-003/DC
Registration number in the Netherlands: RVG 101539, 101452, 101541

26 January 2010

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:	5 October 2009
Concerned Member States:	Decentralised procedure with EL, ES, FI, NO, PT
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 Urquima 75 mg, 150 mg and 300 mg film-coated tablets from URQUIMA S.A. The date of authorisation was on 5 October 2009 in the Netherlands.

The product is indicated for:

- treatment of essential hypertension.
- treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive drug 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 AT_1) 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 decentralised 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 the centralised procedure EU/1/97/049/001-039 by Bristol-Myers Squibb Pharma EEIG since 27 August 1997. Further information can be found in the EPAR of Aprovel (http://www.emea.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 300 mg product is compared with the pharmacokinetic profile of the reference product Aprovel 300 mg tablets registered in the European Union. 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. These generic products can be used instead of their reference products.

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 these product types 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 US Pharmacopoeia. (USP*). The active substance is practically insoluble in water and slightly soluble in alcohol and methylene chloride. The melting point is about 183°C. Irbesartan is not hygroscopic. In literature two polymorphic forms are known. Polymorphic form A is used. The consistency of the polymorphic content of irbesartan was demonstrated in three batches by XRD diffractograms.

The Active Substance Master File (ASMF) procedure is used for 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/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.

Manufacturing process
The drug substance is manufactured in a two step process. The used solvents are ethanol, acetone and ethyl acetate. The drug substance has been adequately characterized and acceptable specifications have been adopted for the solvents and reagents.

Quality control of drug substance
The drug substance specification has been established in-house by the applicant. The specification is acceptable in view of the route of synthesis and the various European guidelines. The consistency of the polymorphic content of Irbesartan was demonstrated in three batches by X-Ray powder diffractograms. Batch analytical data demonstrating compliance with the drug substance specification have been provided for six full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for one full-scale and two pilot-scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (six months). The batches were adequately stored. All parameters tested are considered to be stable, no up or downward trends are observed in any of the examined parameters under both, long-term and accelerated conditions. Based on the stability data provided a retest period of 48 months could be granted.

** USP is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the USA.*

Medicinal Product

Composition
Irbesartan Urquima 75 mg, 150 mg and 300 mg contain as active substance 75, 150 and 300 mg of irbesartan, respectively, and are white, round tablets.

The film-coated tablets are packed in PVC/PVDC-Aluminium blisters.

The excipients are:

Tablet core - lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hypromellose, silica colloidal anhydrous, magnesium stearate.
Film coating – hypromellose, titanium dioxide (E-171), macrogol.

The different strengths are dose proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The dissolution profiles were determined conform the method as described in the USP monograph for irbesartan tablets. The dissolution profiles of the various tablet strengths for one batch of each dose of Irbesartan and of Aprovel® film-coated tablets are obtained, demonstrating similar dissolution profiles for all doses.
The dissolution profiles of the biobatches were demonstrated to be similar as well.

Manufacturing process
The product is manufactured using a wet granulation process, followed by several mixing steps and compressing the final blend into tablets. The manufacturing process has been described in sufficient detail. The polymorphic form does not change during manufacturing. The product is manufactured using conventional manufacturing techniques.

Excipients
The excipients comply with the Ph.Eur. with some additional tests. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, hardness, uniformity of mass, water, dissolution, identity, assay, related substances and microbial contamination. The release and shelf-life specifications are identical. Irbesartan is routinely identified using HPLC analysis where retention time of the main peak must be identical to the reference solution. An alternative way of identification is by TLC. Uniformity of mass has been included in the specifications. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two full-scale batches of each strength and one pilot-scale batch of each strength, demonstrating compliance with the release specification.

Stability tests on the finished product
For the stability a bracketing scheme is applied. Three batches of both the 75 mg and 300 mg strength are included in the stability study. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PVDC-aluminium blisters in outer box. Twelve months long term and six months accelerated data are available.
The studied parameters remain within the specified limits and no significant changes appeared with time. A photostability test was carried out on two pilot scaled batches. The tablets were directly exposed (e.g. without blister) to UV-radiation or directly exposed to visible radiation. No change was observed between the control and the exposed tablets. Since all parameters stay within the shelf-life limits during normal, accelerated and photostability testing and no specific trends are observed, a shelf-life of 24 months without specific storage conditions was granted. The MAH committed to store stability samples of the drug product under long-term conditions (up to 60 months).

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate and magnesium stearate can be seen as potential risk materials with respect to TSE transmittance. A TSE declaration for lactose monohydrate is included in the dossier. Lactose monohydrate is derived from milk from healthy animals. Magnesium stearate is from non-bovine origin.

II.2 Non clinical aspects

These products are generic formulations of Aprovel 75 mg, 150 mg and 300 mg 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 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.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Irbesartan Urquima 300 mg film-coated tablets is compared with the pharmacokinetic profile of the reference product Aprovel 300 mg tablets from the Spanish market.

The choice of the reference product
It is considered to be unnecessary to demonstrate that the dissolution profiles in the various European countries are identical, because the innovator's product is registered by means of central procedure (EU/1/97/049/001-039).

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single dose, open, randomized, 2-way crossover bioequivalence study was carried out under fasted conditions in 29 healthy subjects, aged 18-45 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 after a fasting period of 10 hours. Food was not allowed for 4 hours after dosing and subsequently a standard meal regimen was adopted for the rest of the day. Water ingestion was not allowed till 2 hours after administration. There were 2 dosing periods, separated by a washout period of at least 7 days.

Blood samples were collected predose and at 0.5, 1, 1.25, 1.5, 1.75, 2, 4, 6, 8, 12, 24, 48, 72 and 96 hours after administration of the products.

Analytical/statistical methods
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.

Results
One volunteer was withdrawn from the study due to gastroenteritis (non drug related adverse event). The other 28 subjects (11 male/17 female) completed the study and 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=28	**AUC_{0-120}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	15892 ± 1143	16394 ± 1177	3345 ± 214	1.13	16.5
Reference	17304 ± 1242	17266 ± 1275	3240 ± 232	1.13	14.6
***Ratio (90% CI)**	0.92 (0.86-0.99)	0.96 (0.90-1.02)	1.04 (0.97-1.11)	-	-

CV (%)	16	14	16	-	-

$AUC_{0-\infty}$ 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*

Conclusion
A single-dose study in the fasting state is appropriate from a pharmacokinetic point of view, as the application concerns an immediate release formulation and the reference product can be administered indepently of food. Sampling times were sufficient to cover an adequate description of the pharmacokinetics. Taking into account the elminiation half-life (~15 hours), the MEB considers the washout period acceptable.
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 Urquima 300 mg film-coated tablets 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.

Extrapolation to other strengths
The 75 mg and 150 mg tablets are dose proportional with the 300 mg tablets. The pharmacokinetics of the active substance are linear in the therapeutic dosage range. The different strengths are manfactured by the same manufacturer and manufacturing process. The qualitative composition of the different strenghts is the same and the ratio between amounts of active substance and excipients is also the same. Moreover, the dissolution profiles are comparable. The results of the bioequivalence study performed with the 300 mg tablets therefore apply to the other strengths.

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 postauthorisation 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

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. A total of 20 participants were tested in two rounds with 10 participants each. The test was performed on the English version and all questions were in English. The test person's ability to locate and to understand the information were investigated. Age distribution and the percentage of male and female participants were sufficient. The number of questions was also sufficient. The educational level for each participant was specified. This level was not too high. Both rounds of testing showed that 100% of the participants were able to locate and understand the given information. No adapted version was necessary after the first round. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

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

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. 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 member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Irbesartan Urquima 75 mg, 150 mg and 300 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 2 December 2008. Irbesartan Urquima 75 mg, 150 mg and 300 mg film-coated tablets were authorised in the Netherlands on 5 October 2009.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from December 2008 to December 2011.

The date for the first renewal will be: 31 May 2012

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to store stability samples of the drug product under long-term conditions (up to 60 months).

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
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
TLC	Thin Layer Chromatography
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 batch size of the finished product; downscaling down to 10-fold.	NL/H/1116/ 002-003/IA/ 001	IA	23-11-2009	7-12-2009	Approval	N
Change in batch size of the finished procuct; up to 10-fold compared to the original batch size at the grant of the marketing authorisation.	NL/H/1116/ 003/IA/002	IA	23-11-2009	7-12-2009	Approval	N