CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Irbesartan Jubilant 75 mg, 150 mg and 300 mg, film-coated tablets
Jubilant Pharmaceuticals N.V., Belgium

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/2453/001-003/MR
Registration number in the Netherlands: RVG 104619 - 104621

12 April 2013

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:	26 January 2010
Concerned Member States:	Mutual recognition procedure with 001: DE, SE, UK 002: CY, DE, DK, EE, LT, LV, SE, UK 003: DE, DK, EE, LT, LV, SE, UK
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 Jubilant 75 mg, 150 mg and 300 mg, film-coated tablets, from Jubilant Pharmaceuticals N.V. The date of authorisation was on 26 January 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 product Aprovel 75, 150 and 300 mg film-coated tablets which have been registered through the centralised procedure (EU numbers EU/1/97/046/001-039) by Sanofi Pharma Bristol-Myers Squibb SNC since 27 August 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 150 mg film-coated tablets, registered in the EEA, and obtained from Germany. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for 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. The active substance is a white or almost white crystalline powder which is sparingly soluble in methanol and slightly soluble in methylene chloride, and practically insoluble in water. Irbesartan has five known polymorphic forms and is manufactured as form A. Irbesartan is not hygroscopic and does not exhibit isomerism.

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/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

Manufacturing process
The manufacturing process consists of 3 steps. The last step of the synthesis is a purification step using methanol as organic solvent. No class 1 organic solvents or heavy metal catalysts are used in the manufacturing process. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification established by the MAH is in-line with the monograph of irbesartan published in current edition of European Pharmacopoeia (Ph.Eur.*), with additional requirements for particle size. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for four batches stored at 25°C/60% RH (up to 36 months) and 40°C/75% RH (6 months). No changes are seen under both long-term and accelerated conditions. The proposed retest period of 3 years without additional storage requirements is justified based on the available stability data.

** 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 Jubilant 75 mg film-coated tablets: white to off-white, oval-shaped, film-coated tablets of 11.0 mm with a "**J**" debossed on one side and "**75**" on the other side.

Irbesartan Jubilant 150 mg film-coated tablets: white to off-white, oval-shaped, film-coated tablets of 13.7 mm with a "**J**" debossed on one side and "**150**" on the other side.

Irbesartan Jubilant 300 mg film-coated tablets: white to off-white, oval-shaped, film-coated tablets of 17.3 mm with a "**J**" debossed on one side and "**300**" on the other side.

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

The excipients are:
Tablet core: Lactose monohydrate, Silica colloidal anhydrous (E551), Microcrystalline cellulose (E460), Croscarmellose sodium (E468), Hypromellose (E464), Pregelatinized starch, Magnesium stearate (E572).
Film-coating: Lactose monohydrate, Hypromellose (E464), Macrogol 4000, Titanium dioxide (E171).

The tablets are fully dose proportional.
The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The MAH performed characterization of the innovator product, selection of the dissolution method and optimisation of the choice and amount of excipients. The container closure system was based on the innovator's and wet granulation was chosen as manufacturing process. Comparative dissolution profiles of the different strengths of the innovator and the proposed drug product demonstrate essential similarity with more than 95% dissolved in 10 minutes in 0.1N HCl. The comparative dissolution profiles at pH 4.5 and pH 6.8 were considered to be similar as well. The batches used in the BE study are used for process validation as well. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The tablets are manufactured by sifting, dry mixing and granulation, followed by further drying, sifting and milling. The binder solution is added, the wet mass is sifted, dried and milled. The granules are then blended, compressed, film-coated and packed. 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 and therefore, process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with their respective Ph.Eur. monograph with additional tests. The coating material Opadry II white OY-L-28900 is controlled in-house. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification, water content, uniformity of dosage units, dissolution, assay, related substances and microbial limits. The release and shelf-life limits are identical, except for water content, and acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on six pilot-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided six pilot scaled batches stored at 25°C/60%RH (12 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PVdC-Alu blisters. Under both storage conditions an increase in water content is observed.
A photostability study has been performed in line with the NfG on photostability testing (ICH Q1B). The tablets were directly exposed to 1.2 million lux hours and 200-watt hours/square meter. No significant changes were observed for the tested parameters assay, related substances and dissolution, demonstrating the photostability of the drug product.
The proposed shelf-life of 24 months can be granted with the storage condition 'Store in the original package to protect from moisture. This medicinal product does not require any special temperature storage conditions.'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate and magnesium stearate are of animal origin. TSE/BSE statements have been provided stating compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products.

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 an overview of pharmacokinetics, pharmacodynamics, clinical efficacy and clinical safety reference is made tot the EPAR on the reference product Aprovel.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Irbesartan Jubilant 150 mg, film-coated tablets (Jubilant Pharmaceuticals N.V., Belgium) is compared with the pharmacokinetic profile of the reference product Aprovel 150 mg film-coated tablets (Sanofi Pharma Bristol-Myers Squibb SNC, Germany).

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, open-label, two-way crossover study with the Irbesartan Jubilant 150 mg test product and Aprovel 150mg as reference product to show bioequivalence. A total of 54 healthy male volunteers, aged 18-41 years, participated in the pharmacokinetic study. The formulations were administered with 240 ml water under fasting conditions. For each subject there were 2 dosing periods, separated by a washout period of 10 days.

Blood samples were collected pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours after administration of the products in each of two periods.

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
The drop-out subjects are explained below:

- Three subjects dropped out before dose administration in period I as they had a lower pre-dose blood pressure than recommended.
- Two subjects dropped out after adverse drug events (unlikely related to drug administration) in period I.
- One subject dropped out after adverse drug event (possibly related to drug administration).
- One subject withdrew consent in period I after he had a coughing reflex, the study drug came out from the mouth and he did not swallow it.
- One subject withdrew consent before dose administration in period II

Only the samples of the 46 volunteers who completed the study were to be analysed.

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

Treatment N=46	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	9885 (± 4072)	11032 (± 4739)	3259 (± 1164)	1.250 (0.5- 4.5)	- 4.7 (± 4.9)
Reference	9974 (± 3400)	11023 (± 3802)	2872 (± 954)	1.250 (0.5- 4.0)	5.3 (±7.1)
***Ratio (90% CI)**	0.97 (0.92-1.03)	0.97 (0.91-1.04)	1.13 (1.04-1.22)	-	-
CV (%)	17.12	18.38	23.52	-	-

$AUC_{0-\infty}$ 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 Jubilant 150 mg, film-coated tablets and Aprovel 150 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 75 mg and 300 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 bioequivalence study should in general be conducted at the highest strength. For products with linear pharmacokinetics and where the drug substance is highly soluble, selection of a lower strength than the highest is also acceptable. This is applicable for irbesartan.

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 mutual recognition procedure is almost similar to the SPC of the innovator Aprovel. However, several sections of the SPC of Aprovel have recently been updated. These changes have been adopted.

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 was performed in the UK. Participants for this test were selected to approximate the demographics of the British population.

The questions were open and participants were encouraged to respond in their own words. A pilot round was performed with 2 participants, followed by 2 rounds with 10 participants each. The results were evaluated after each round.

According to the outcome of the test, no weaknesses have been identified. The answers to all questions could (quite) easily be found and the information found could be (quite) easily understood.

From the general questions (regarding the format of the PL) the main point of concern for some of the test participants was that certain parts of the leaflet were too long and complex. According to the MAH the length of the leaflet cannot be shortened without jeopardizing its content and validity, as the leaflet must be an accurate representation of the SPC and convey all its proper safety issues and warnings.

In general the RMS agrees with the conclusions that the test is acceptable, however the RMS suggested to shorten section 1 of the PL. This suggestion has been adopted.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Irbesartan Jubilant 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, film-coated 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 is consistent with that of the reference product. 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 Jubilant 75 mg, 150 mg and 300 mg, film-coated tablets were authorised in the Netherlands on 26 January 2010.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Irbesartan Jubilant 75 mg, 150 mg and 300 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 9 September 2012.

The date for the first renewal will be: 27 July 2015.

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

Quality - medicinal product

- The MAH committed to re-evaluate the release and shelf-life specifications for water content at the end of the stability study.

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