CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Irbesartan Ranbaxy 75 mg, 150 mg and 300 mg, film-coated tablets Ranbaxy Belgium NV, 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/1242/001-003/DC
Registration number in the Netherlands: RVG 101336, 101338, 101339

22 March 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:	7 August 2009
Concerned Member States:	Decentralised recognition procedure with BE, BG, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LV, NO, PL, PT, RO, SE, SI, SK, 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 Ranbaxy 75 mg, 150 mg and 300 mg, film-coated tablets, from Ranbaxy Belgium NV. The date of authorisation was on 7 August 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 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 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 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 Karvea (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 product is compared with the pharmacokinetic profile of the reference product Aprovel 300 mg, registered in France. 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 medicinal product.

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 insoluble in water at different pHs. In literature two polymorphic forms are known. Polymorphic form A is used.

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 four step process. A flow chart and short description of the manufacturing process is included. The structure of the drug substance has been adequately elucidated.

Quality control of drug substance
The drug substance specification is in line with the USP, with additional requirements for residual solvents and particle size distribution. 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 three production scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for three production scaled batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). At accelerated storage conditions no changes were observed. At long term storage conditions also no changes or trends were observed. The claimed shelf life of four years is justified, with no special storage conditions are required.

** 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 Ranbaxy 75 mg,150 mg and 300 mg contain as active substance 75 mg, 150 mg and 300 mg of irbesartan, respectively, and are white to off white, film coated oval shaped, biconvex tablets debossed with 'I3' on one side and plain on the other.

The film-coated tablets are packed in clear transparent PVC/PE/PVdC/aluminium foil blisters.

The excipients are:

Tablet core	*Film-coating (Opadry II OY-LS-28900 White)*
lactose monohydrate	lactose monohydrate
microcrystalline cellulose	hypromellose

croscarmellose sodium
hypromellose
anhydrous colloidal silica
magnesium stearate
titanium dioxide
macrogol 4000

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 compatibility of the excipients with the drug substance is determined.
The solubility of irbesartan at different pH's was investigated. The lower the pH, the better irbesartan dissolves. The dissolution profiles of innovator and test product were determined. The dissolution profiles are comparable at all pH, but complete dissolution is observed at pH 1.0 only. The impurity profiles of test and innovator product are also comparable. A bioequivalence study was performed using innovator product Aprovel 300 mg.

Manufacturing process
The manufacturing consist of several mixing steps, after which the final blend is compressed into tablets. The manufacturing process has been described in sufficient detail. The polymorphic form does not change during manufacturing. Process validation data on the product has been presented for two pilot scaled batches of each strength. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post authorisation.

Quality control of drug product
The product specification includes tests for appearance, identity, assay, degradation, uniformity of dosage units, water content, dissolution, disintegration and microbial quality. The release and shelf life requirements are identical, except for dissolution. The analytical methods have been adequately described and validated. Batch analytical data have been provided on two production scale batches of each strength, demonstrating compliance with the release specification.

Stability tests on the finished product
Stability data on the product has been provided two batches of each strength stored at 25°C/60% RH (18 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 transparent PVC/PE/PVdC blisters, Aclar blister and a bulk shipment pack.
Under all conditions variability in assay and a slight increase in water content is observed. Furthermore, for the two lower strengths a slight increase in two impurities is observed. No other trends or changes have been observed. The polymorphic form does not change during storage. A photostability study has been performed and results show that the drug product is unstable with respect to light. Therefore the storage condition "store in the original package to protect from light" is applicable. Based on the stability data provided, the claimed shelf-life of 24 months could be granted. The MAH committed to submit the results of the ongoing stability studies.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose is derived from milk for human consumption and for magnesium a TSE-CEP has been provided. There are no other 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

These products are generic formulations of Karvea 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 Ranbaxy 300 mg film-coated tablets (Ranbaxy Belgium NV) is compared with the pharmacokinetic profile of the reference product Aprovel 300 mg tablets (Sanofi Pharma, BMS France).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.

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

Design
An open label, randomized, 2-treatment, 2-period, 2-sequence, single dose, crossover bioequivalence study was carried out under fasted conditions in 28 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 after a fasting period of 10 hours. There were 2 dosing periods, separated by a washout period of at least 7 days. Standard meals (lunch, snack and dinner) were provided at 4, 9 and 13 hours post-dose. Drinking water was not allowed 1 hour pre-dose to 2 hours post-dose; thereafter it was allowed at all times.
Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 12, 16, 24, 36 and 48 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
Two volunteers were withdrawn due to adverse events (vomiting, nausea, fever and loose stools). The other 26 subjects 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=26	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	12167.9 ± 3628.2	12612.4 ± 3690.0	2536.3 ± 781.2	1.7 ± 0.9	8.0 ± 4.2
Reference	12738.5 ± 4451.7	13413.5 ± 4489.9	2685.1 ± 850.4	1.9 ± 1.2	7.6 ± 2.5
***Ratio (90% CI)**	0.96 (0.90-1.03)	0.95 (0.88-1.03)	0.94 (0.86-1.03)	-	-
CV (%)	15	16	19	-	-

$AUC_{0-\infty}$	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 Ranbaxy 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.

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
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. 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. The test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The technical readability, comprehensibility of the text, traceability of information and the applicability were investigated. Age distribution, pecentage male and female and were sufficient. The educational level varied from secondary school completion to university graduates.
Based on the results of from the first round, no revisions to the PIL were made. The second round of testing on the revised PIL showed that 100% of the participants were able to find the correct information, and at least 90% were able to answer the questions correctly. There were sufficient questions about the critical sections. Overall, the readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Irbesartan Ranbaxy 75 mg, 150 mg and 300 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Karvea 75 mg, 150 mg and 300 mg tablets. Karvea tablets 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.

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 Ranbaxy 75 mg, 150 mg and 300 mg, film-coated tablets with the reference products, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 11 December 2008. Irbesartan Ranbaxy 75 mg, 150 mg and 300 mg, film-coated tablets were authorised in the Netherlands on 7 August 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: December 2013.

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

Quality - medicinal product

- The MAH committed to submit the results of the ongoing stability studies covering the whole shelf-life.

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
Withdrawal of marketing authorisation in Slovenia	--	--	--	13-5-2009	Approval	N
Withdrawal of marketing authorisation in Latvia	--	--	--	11-6-2009	Approval	N