CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Vilconir 75 mg, 150 mg, and 300 mg film-coated tablets Pharma Resources Dr. Schluttig GmbH, Germany

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/1686/001-003/DC
Registration number in the Netherlands: RVG 104947,104950,104951

3 May 2010

Pharmacotherapeutic group:	angiotensin II antagonists, plain
ATC code:	C09CA04
Route of administration:	oral
Therapeutic indication:	essentail hypertension; renal disease in patients with hypertension and type 2 diabetes mellitus
Prescription status:	prescription only
Date of authorisation in NL:	22 February 2010
Concerned Member States:	Decentralised procedure with DE and 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 Vilconir 75 mg, 150 mg, and 300 mg film-coated tablets, from Pharma Resources Dr. Schluttig GmbH. The date of authorisation was on 22 February 2010 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 film-coated tablets which have been registered through centralised procedure EU/1/97/046 by Sanofi Pharma Bristol-Myers Squibb SNC since 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 product is compared with the pharmacokinetic profile of the reference product Aprovel 300 mg, 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. 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 generic medicinal products.

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 United States Pharmacopoeia (USP*). The active substance is practically insoluble in water. Irbesartan has five known polymorphic forms and is manufactured as form A. Irbesartan is not hygroscopic and has no potential 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/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.

Manufacture
ASM 1 - The manufacturing process consists of 6 steps from which the last step is a purification step. The starting materials and solvents have been described adequately. No class 1 solvents or metal catalysts are used in the manufacturing process. The active substance has been adequately characterized. The specifications that have been adopted for the starting material, solvents and reagents are acceptable.

ASM 2 - The manufacturing process consists of 3 steps. The last step of the synthesis is a purification step. 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.

ASM 3 - The manufacturing process consists of 5 steps of which the last step is a purification step. No class 1 organic solvents are used. 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 is has been established in-house by the MAH, 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 for each supplier.

Stability of drug substance
ASM 1 - Stability data on the active substance have been provided for three full-scale batches from one manufacturing site stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months), and for three full-scale batches from another manufacturing site stored at 25°C/60% RH (9 months) and 40°C/75% RH (6 months). The batches were adequately stored. No changes or trends are seen from the stability data at both conditions and from both manufacturing sites. The proposed retest period of 24 months for the drug product when kept on the original package is justified.

ASM 2 - 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). The batches were adequately stored. 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.

ASM 3 - Stability data on the active substance have been provided for 3 full-scale batches stored at 25°C/60% RH (48 months) and 40°C/75% RH (6 months). The batches were adequately stored. No changes or trends are seen under both conditions. The proposed retest period of 60 months without additional storage requirements is acceptable.

** 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
The products are formulated as film-coated tablets which are packaged in PVC/PVDC/Aluminium blisters. Three strengths are developed: Vilconir 75 mg, 150 mg, and 300 mg tablets containing 75 mg, 150 mg or 300 mg irbesartan, respectively.

Vilconir 75 mg are are white, biconvex, oval-shaped, film-coated tablets with a length of approximately 10 mm.
Vilconir 150 mg are are white, biconvex, oval-shaped, film-coated tablets with a length of approximately 13 mm.
Vilconir 300 mg are are white, biconvex, oval-shaped, film-coated tablets with a length of approximately 16 mm.

The excipients are:
Tablet core: lactose monohydrate, maize starch pregelatinized, copovidone, croscarmellose (E468), colloidal anhydrous silica (E551), and magnesium stearate (E470b).
Film-coating: hypromellose (E464), macrogol 400, and titanium dioxide (E171).
The excipients and packaging are usual for this type of dosage form.

The tablets do not bear a score-line. The different strenghts are dose proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were regarding tablet hardness, influence of active substance on particle size and comparative dissolution studies. The choices of the packaging and manufacturing process are justified. The batch used in the bioequivalence studies was manufactured according to the finalized formulation and manufacturing process. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of mixing, dry granulation / pre-compression, sieving / milling, mixing, compression and film-coating. 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 per strength from one manufacturing site and three pilot-scale batches at the other manufacturing site. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Excipients
The excipients comply with the Ph.Eur. requirements. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, average mass, disintegration, identity, assay, uniformity of dosage units, dissolution and related substances. The release requirements are identical to the shelf-life specifications. The proposed specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production sites have been provided on two pilot-scale batches per strength and at least two smaller batches per strength demonstrating compliance with the release specification.

Photostability
The MAH performed photostability testing in accordance with the *NfG on the Photostability Testing of New Active Substances and Medicinal Products* on one batch of drug product of every strength. The results show that the tested parameters appearance, assay and degradation products do not change upon light exposure. Therefore, no additional storage requirements are needed for the drug product.

Microbiological Attributes
Microbiological attributes according to the current Ph.Eur.* requirements have been tested on pilot-scale batches and all results comply. The test is also part of the stability program. This is acceptable.

Stability tests on the finished product
Stability data on the product has been provided for two pilot-scale batches and one smaller batch per strength for one manufacturing site, stored at 25°C/60% RH (max. 12 months), 30°C/65% RH (max. 12 months) and 40°C/75% RH (max. 6 months). For the other manufacturing site stability data on two pilot-scale batches per strength have been provided stored at 25°C/60% RH (6 months), 30°C/65% RH (6 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/Al-blisters. Except for an increase in impurities mainly at accelerated conditions, no changes or trends are observed. All tested parameters remain within the specified limits. The proposed shelf-life of 24 months without any additional storage requirement is justified.
Ongoing stability studies will be continued up to 60 months long-term according to the stability protocol. A post-approval stability study will be performed on production scale batches. These commitments are noted and results of the ongoing stability study at least up to the proposed retest period are awaited as soon as available.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is of animal origin. A TSE declaration is 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.

** 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.*

II.2 Non clinical aspects

This product is a generic formulation of Aprovel, 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 one bioequivalence study in which the pharmacokinetic profile of the test product Vilconir 300 mg film-coated tablets (Pharma Resources Dr. Schluttig GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Aprovel 300 mg film-coated tablets (Sanofi-Aventis, France).

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

Study design
A single-dose, randomised, open-label, 2-way, crossover, bioequivalence study was carried out under fasted conditions in 36 (26 males, 8 females) healthy, non-smoking, volunteers of non-childbearing potential. The subjects were aged 21-55; thirty-one have a Caucasian ethnic background, one Black and two American Indian. Vital sign measurement and laboratory evaluation was performed.
Each subject received a single dose (300 mg) of one of the 2 irbesartan formulations.The tablets were orally administered with 240 ml water after a fasting period of at least 10 hours. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected predose and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0, 24.0, 36.0, 48.0 and 72.0 hours after administration of the products.
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.

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*.

Results
Three subjects were replaced with stand-by subjects prior to dosing; one because of out of range vital signs; one because of nausea following catheter insertion, and one because of difficulties with catheter insertion. Furthermore two subjects were withdrawn during period one (both reference product) due to personal reasons, and due to a positive drug screen result. Both subjects were therefore excluded from pharmacokinetic and statistical analysis.
Two samples were discarded and excluded from analysis because of insufficient blood volume. Three subjects deviated from the protocol, but samples were not excluded from analysis. These deviations were consumption; of chocolate (one subject, between t=36 and t=48), chocolate cake (one subject, between t=24 and t=36), a cola drink (one subject, 36 hours pre-dose) and Nutella (one subject, between t=24 and t=36).
Thirty-four subject 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=34**	**AUC_{0-t}*** **ng.h/ml**	**$AUC_{0-\infty}$*** **ng.h/ml** **N=33**	**C_{max}*** **ng/ml**	**t_{max}** **h**	**$t_{1/2}$** **h** **N=33**
Test	18403 ± 6451	19439 ± 6477	3003 ±782	1.84 ± 0.75	13.57 ± 5.50
Reference	17253 ± 5438	18222 ± 5543	3215 ±763	1.33 ± 0.67	12.73 ± 5.72
***Ratio (90% CI)**	1.06 (1.01-1.12)	1.06 (1.01-1.12)	0.93 (0.88-0.98)	---	---
CV (%)	12.9	12.9	13.6	---	---

$AUC_{0-\infty}$ 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 Vilconir 300 mg film-coated tablets and the 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 strenghts

The active substance is produced by the same manufacturer for all strengths and exhibits linear pharmacokinetic properties. The quantitative composition for all strengths is similar, as is the ratio between active substance and excipients. Dissolution profiles are comparable as well. 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

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Aproval marketed by Sanofi Pharma Bristol-Myers Squibb SNC .

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.
After two introduction questions, there were 14 questions about the content and they address the key safety issues. The questions cover the areas, locate information in the package leaflet, understand it and know how to act on it.
After a pilot test with 3 subjects, two rounds with each 10 subjects were undertaken. They were spread on sex and education quotas, but the age was not well spread. There was only one participant of 45 years of age and there were no older participants. Irbesartan will however be used by older people as well. The participants were selected from a database of the testing company by using defined inclusion and exclusion criteria.
The duration of each interview was between 15 and 25 minutes. All interviews were held by one trained and empathetic interviewer with good knowledge of medicine. In addition to the questions on content, the subjective impression of the participants is evaluated with the following questions: Comprehensibility, font size and design, layout and organisation. The font size of the leaflet was given a good subjective rating by the participants: 7.8 out of a possible 10. This indicates that the legibility of the font was satisfactory for most participants. The subjective rating of 7.2 out of a possible 10 indicates that most participants were satisfied with the leaflet overall. The comprehensibility score was 7.3 out of a possible 10. This score indicates that most participants were satisfied with the style of writing used in the leaflet.
There was only one participant who could not find the answer to one question, all the other pieces of information were found by the remaining participants. There was also only one participant who did not understand or only understood sufficiently the answer to one question, but the participant did admit that she is dyslexic.
The results of the interviews showed that the PIL for Irbesartan STADA 75 mg, 150 mg, 300 mg film-coated tablets could be rated as readable and comprehensible according to the requirements of the European directive with a Dependent Readability Index of 100.0 and an Independent Readability Index of 100.0. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Vilconir 75 mg, 150 mg, and 300 mg film-coated tablets have a proven chemical-pharmaceutical quality and are a generic form 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.

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 Vilconir 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 11 January 2010. Vilconir is authorised in the Netherlands on 22 February 2010.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from 11 January 2010 to 11 January 2013.

The date for the first renewal will be: 11 September 2013.

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

Quality - medicinal product

- The MAH has committed to perform post-approval validation on three production batches from both manufacturing sites according to the same validation scheme as used for the pilot-scale batches.
- The MAH has committed to continue ongoing stability studies up to 60 months long-term according to the stability protocol. In addition, a post-approval stability study will be performed on production-scale batches. Results of the ongoing stability study at least up to the proposed retest period will be provided when available.

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