CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Irbesartan Unichem 150 mg and 300 mg, film-coated tablets
Unichem Laboratories Limited, Ireland

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/2568/001-002/DC
Registration number in the Netherlands: RVG 111389-111390

2 May 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 authorisation in NL:	11 February 2013
Concerned Member States:	Decentralised procedure with DE, IE, 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 Unichem 150 mg and 300 mg, film-coated tablets from Unichem Laboratories Limited. The date of authorisation was on 11 February 2013 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 decentralised procedure concerns a generic application claiming essential similarity with the innovator products Aprovel 150 mg and 300 mg tablets which have been registered through centralised procedure EU/1/97/049/001-003 by Bristol-Myers Squibb Pharma EEIG since 1997.
Further information can be found in the EPAR of Aprovel (http://www.ema.europa.eu/htms/human/epar/).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Aprovel 300 mg tablets, registered in the EEA. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

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

No scientific advice has been given to the MAH with respect to these products.

No paediatric development programme has been submitted as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is irbesartan, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Irbesartan is a white to almost white, crystalline powder, which is practically insoluble in water, sparingly soluble in methanol, and slightly soluble in methylene chloride. The substance is not hygroscopic. No asymmetric carbon atoms are present in Irbesartan. Polymorphic form A is produced.

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 synthesis of irbesartan is a six-step process. The structure has been adequately elucidated and acceptable specifications of the starting materials have been adopted.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. monograph of irbesartan with additional requirements for residual solvents, polymorphic form and synthesis impurities. The specification is acceptable in view of the route of synthesis and the various European guidelines. The MAH has also included a test for particle size distribution with acceptable limits. Batch analytical data demonstrating compliance with the drug substance specification has been provided for three commercial-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for seven commercial-scale batches stored at 25°C/60% RH (one batch up to 36 months, two batches up to 26 months, one up to 18 months and three batches up to 12 months) and at 40°C/75% RH (seven batches up to 6 months). The stability data shows no out of specifications. A slight upward trend in water content is observed in accelerated conditions. The re-test period of 24 months can be granted based on the results. The storage restriction of "store below 30°C" is not considered necessary, but can be adopted.

** 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 Unichem 150 mg is a white to off-white coloured, oval shaped, biconvex, film-coated tablet with "U" debossed on one side and "I" debossed on the other side.
Irbesartan Unichem 300 mg is a white to off-white coloured, oval shaped, biconvex, film-coated tablet with "U" debossed on one side and plain on the other side.

The film-coated tablets are packed in white opaque PVC/PVdC-Aluminium blister packs.

The excipients are:
Tablet core - mannitol (E421), croscarmellose sodium, colloidal anhydrous silica (E551), poloxamer 188, magnesium stearate (E572)
Film-coating - Opadry white 03B28796 which contains: hypromellose (E464), titanium dioxide (E171) , macrogol.

The two tablet strengths are dose proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Development studies regarding the granulation process followed by direct compression and subsequent optimisation of excipient concentrations were performed. The drug product batch used in the bioequivalent study has been manufactured with the commercial formulation according to the commercial manufacturing process. Dissolution profiles of the test batch and the reference product used in the bioequivalence study in three media at five time points were determined. Similarity was demonstrated. The pharmaceutical development of the product has been adequately performed. The biowaiver for the additional strength has been justified and on quality grounds the similarity of test and reference product has been shown.

Manufacturing process
The manufacturing process is a standard process, consisting of mixing, wet granulation, wet milling, drying of granules, sifting and sizing of granules, lubrication, compression and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three smallest commercial scale batches of each strength. The product is manufactured using conventional manufacturing techniques. Process validation for the largest commercial scale batches will be performed post authorisation.

Control of excipients
The excipients comply with Ph.Eur. requirements or in-house specification (Opadry coating agent). These specifications are acceptable and several functionality-related requirements as stated in the Ph.Eur. monographs have been adopted for several excipients. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, average mass, identification, uniformity of dosage units, disintegration, dissolution, loss on drying, assay, related substances and microbial purity. Shelf-life requirements are identical to release limits, except for loss on drying. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three smallest commercial scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on three smallest commercial scale batches of each strength stored at 25°C/60% RH (up to 18 months) and 40°C/75% RH (up to 6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in white opaque PVdC/PVC-Aluminium blisters or bulk packaging. No out-of-specifications or obvious trends were observed. Photostability testing was part of a forced degradation study, and degradation was not observed. The product is therefore not considered sensitive to light. The proposed shelf-life period of 24 months is justified. No specific storage conditions are necessary.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a generic formulation of Aprovel, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of irbesartan released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Irbesartan is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Irbesartan Unichem 300 mg (Unichem Laboratories Limited, Ireland) is compared with the pharmacokinetic profile of the reference product Aprovel 300 mg tablets (Sanofi Pharma Bristol-Myers Squibb, France).

The choice of the reference product
The reference product is acceptable, as Aprovel is registered through the centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 18-45 years. Each subject received a single dose (300 mg) of one of the 2 irbesartan formulations. There were 2 dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, 36, 48 and 72 hours after administration of the products.

This design is acceptable and according to the guideline. The sampling scheme is long enough and the frequency high enough to adequately estimate pharmacokinetic parameters.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
There were two drop-outs since they did not report for the second study period. Therefore, 26 subjects were included in pharmacokinetic and statistical analysis.

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

Treatment	AUC_{0-t} µg/ml/h	$AUC_{0-\infty}$ µg/ml/h	C_{max} µg/ml	t_{max} h
Test	19.9 ± 4.4	20.2 ± 4.4	4.4 ± 1.5	2.0 (1.0 – 5.0)
Reference	21.2 ± 6.0	21.4 ± 6.1	4.2 ± 1.2	1.5 (0.75 – 5.0)
***Ratio (90% CI)**	0.96 (0.89-1.03)	0.96 (0.89-1.03)	1.04 (0.96-1.14)	--

$AUC_{0-\infty}$ 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

**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 Unichem 300 mg and Aprovel 300 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Irbesartan may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of irbesartan. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Extrapolation to 150 mg strength
The requirements for waiving bioequivalence studies mentioned in the guideline are fulfilled. This means that:
- the pharmaceutical products are manufactured by the same manufacturer and process
- the pharmacokinetics has been shown to be linear over the therapeutic range
- the qualitative composition of the different strengths is the same
- the ratio between amounts of active substance and excipients is the same
- the dissolution profile is similar under identical conditions for the additional strength and the strength of the biobatch.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan
Irbesartan was first approved in 1997, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of irbesartan can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

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

Readability test

The package leaflet has 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 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. In total 100% of the participants were able to locate the information in the package leaflet and the overall percentage of correct answers was 100%. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Irbesartan Unichem 150 mg and 300 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Aprovel 150 mg and 300 mg tablets. Aprovel is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other irbesartan containing products.

The Board followed the advice of the assessors.

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 Unichem 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 18 December 2012. Irbesartan Unichem 150 mg and 300 mg, film-coated tablets were authorised in the Netherlands on 11 February 2013.

The date for the first renewal will be: 18 December 2017.

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

<u>Quality – medicinal product</u>

- The MAH committed to re-evaluate the limit for loss on drying at end of shelf-life when this data becomes available.
- The MAH committed to perform comparative dissolution testing on the first three large-scale production batches vs. the bio-batch.
- The MAH committed to validate three drug product large-scale batches of each strength on commercial scale.
- The MAH committed to provide stability data up to 24 months in order to fully establish this 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