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Public Assessment Report

Name of the Product:

Irbesartan Elpen

75 mg, 150 mg, 300 mg film-coated tablet

(irbesartan)

Procedure number: HU/H/0412/001-003/DC

Marketing authorisation holder: Elpen Pharmaceutical Co. Inc.

Date: 7 June 2016

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Irbesartan Elpen (in Germany: Irbesartan Aenorasis) 75 mg, 150 mg and 300 mg film-coated tablets. In the reference member state the holder of the marketing authorisation is Elpen Pharmaceutical Co. Inc.

The active substance is irbesartan. The film-coated tablets contain 75 mg or 150 mg or 300 mg irbesartan.

The other ingredients are microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, silica colloidal anhydrous, magnesium stearate, hypromellose, polyvinyl alcohol (partially hydrolysed), macrogol/polyethylene glycol 3350, titanium dioxide (E171) and talc.

The film-coated tablets are white and oval-shaped. They are supplied in blister packs or unidose blister packs.

The active substance irbesartan belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin-II is a substance produced in the body which binds to receptors in blood vessels causing them to tighten. This results in an increase in blood pressure. Irbesartan Elpen prevents the binding of angiotensin-II to these receptors, causing the blood vessels to relax and the blood pressure to lower. Irbesartan Elpen slows the decrease of kidney function in patients with high blood pressure and type 2 diabetes.

Irbesartan Elpen is used in adult patients:
- to treat high blood pressure (essential hypertension),
- to protect the kidney in patients with high blood pressure, type 2 diabetes and laboratory evidence of impaired kidney function.

What patients need to know before taking Irbesartan Elpen?

Those who
- are allergic to irbesartan or any other ingredients of this medicine,
- are more than 3 months pregnant. (It is also better to avoid Irbesartan Elpen in early pregnancy – see pregnancy section),
- have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren .

must not take Irbesartan Elpen.

Warnings and precautions

Patients to whom any of the following apply should consult their doctor before taking Irbesartan Elpen:
- they get excessive vomiting or diarrhoea;

- they suffer from kidney problems;
- they suffer from heart problems;
- they receive Irbesartan Elpen for diabetic kidney disease. In this case the doctor may perform regular blood tests, especially for measuring blood potassium levels in case of poor kidney function;
- they are going to have an operation (surgery or be given anaesthetics;
- they are taking any of the following medicines used to treat high blood pressure:
  - an ACE-inhibitor (for example enalapril, lisinopril, ramipril) in particular if having diabetes-related kidney problems,
  - aliskiren.

The doctor may check the kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in the blood at regular intervals.

Patients must tell their doctor if they think they are or might become pregnant. Irbesartan Elpen is not recommended in early pregnancy, and must not be taken if the patient is more than 3 months pregnant, as it may cause serious harm to the baby if used at that stage.

Children and adolescents

This medicinal product should not be used in children and adolescents because the safety and efficacy have not yet been fully established.

Other medicines and Irbesartan Elpen

The doctor should be informed if the patient is taking, have recently taken or might take any other medicines. The doctor may need to change the dose and/or to take other precautions if the patient is taking an ACE-inhibitor or aliskiren.

The patient may need to have blood checks if taking:
- potassium supplements,
- salt substitutes containing potassium,
- potassium-sparing medicines (such as certain diuretics),
- medicines containing lithium.

If taking certain painkillers, called non-steroidal anti-inflammatory drugs, the effect of irbesartan may be reduced.

Irbesartan Elpen with food and drink

Irbesartan Elpen can be taken with or without food.

Pregnancy and breast-feeding

Patients must tell their doctor if they think they are (or might become) pregnant. The doctor will normally advise to stop taking Irbesartan Elpen before becoming pregnant or as soon as

the patient knows she is pregnant and will advise her to take another medicine instead of Irbesartan Elpen, for this medicinal product is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to the baby if used after the third month of pregnancy.

Patients must tell their doctor if they are breast-feeding or about to start breast-feeding. Irbesartan Elpen is not recommended for mothers who are breast-feeding, and the doctor may choose another treatment for those who wish to breast-feed, especially if the baby is new-born, or was born prematurely.

Driving and using machines

No studies on the effects on the ability to drive and use machines have been performed. Irbesartan Elpen is unlikely to affect the ability to drive or use machines. However, occasionally dizziness or weariness may occur during treatment of high blood pressure. If somebody experiences these, he/she should consult the doctor before attempting to drive or use machines.

Irbesartan Elpen contains lactose.

Those who have been told by their doctor that they have an intolerance to some sugars (e.g. lactose), should contact the doctor before taking this medicine.

How to take Irbesartan Elpen

Irbesartan Elpen is for oral use.

The tablet(s) should be swallowed with a sufficient amount of fluid (e.g. one glass of water).

Irbesartan Elpen may be taken with or without food.

It is advised to take the daily dose at about the same time each day. It is important that the patients continues to take Irbesartan Elpen until the doctor tells otherwise.

– *Patients with high blood pressure*
  The usual dose is 150 mg once a day (two 75 mg tablets or one 150 mg tablet a day). The dose may later be increased to 300 mg (four 75 mg tablets or two 150 mg tablets or one 300mg tablet a day) once daily depending on blood pressure response.

– *Patients with high blood pressure and type 2 diabetes with kidney disease*
  In patients with high blood pressure and type 2 diabetes, 300 mg (four 7 5mg tablets or two 150 mg tablets or one 300 mg tablet a day) once daily is the preferred maintenance dose for the treatment of associated kidney disease.

The doctor may advise a lower dose, especially when starting treatment in certain patients such as those on haemodialysis, or those over the age of 75 years.

The maximal blood pressure lowering effect should be reached 4-6 weeks after beginning treatment.

Use in children and adolescents

Irbesartan Elpen should not be given to children under 18 years of age. If a child swallows some tablets, the doctor must be contacted immediately.

What to do if more Irbesartan Elpen has been taken that it should have been?

If somebody accidentally takes too many tablets, the doctor must be contacted immediately.

What to do i taking Irbesartan Elpen has been forgotten?

If a daily dose has been accidentally missed, the next dose should be taken as normal. A double dose should not be taken to make up for a forgotten dose.

Possible side effects

Like all medicines, Irbesartan Elpen can cause side effects, although not everybody experiences them. Some of these effects may be serious and may require medical attention.

As with similar medicines, rare cases of allergic skin reactions (rash, urticaria), as well as localised swelling of the face, lips and/or tongue have been reported in patients taking irbesartan. If the patient gets any of these symptoms or gets short of breath, must stop taking Irbesartan Elpen and contact the doctor immediately.

The frequency of the side effects listed below is defined using the following convention: Very common: may affect more than 1 in 10 people
Common: may affect up to 1 in 10 people Uncommon: may affect up to 1 in 100 people

Side effects reported in clinical studies for patients treated with Irbesartan Elpen were:
- very common (may affect more than 1 in 10 people): if the patient suffers from high blood pressure and type 2 diabetes with kidney disease, blood tests may show an increased level of potassium;
- common (may affect up to 1 10 people): dizziness, feeling sick/vomiting, fatigue and blood tests may show raised levels of an enzyme that measures the muscle and heart function (creatine kinase enzyme). In patients with high blood pressure and type 2 diabetes with kidney disease, dizziness when getting up from a lying or sitting position, low blood pressure when getting up from a lying or sitting position, pain in joints or muscles and decreased levels of a protein in the red blood cells (haemoglobin) were also reported;

– uncommon (may affect up to 1 in 100 people): heart rate increased, flushing, cough, diarrhoea, indigestion/heartburn, sexual dysfunction (problems with sexual performance), chest pain.

Some undesirable effects have been reported since marketing of Irbesartan Elpen. These undesirable effects where the frequency is not known are: feeling of spinning, headache, taste disturbance, ringing in the ears, muscle cramps, pain in joints and muscles, abnormal liver function, increased blood potassium levels, impaired kidney function, and inflammation of small blood vessels mainly affecting the skin (a condition known as leukocytoclastic vasculitis). Uncommon cases of jaundice (yellowing of the skin and/or whites of the eyes) have also been reported.

How to store Irbesartan Elpen

Store it below 25°C.

Keep this medicine out of the sight and reach of children.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Irbesartan Elpen 75 mg, 150 mg and 300 mg film-coated tablets. The procedure was finalised at 12 February 2016. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, an application has been submitted to the reference and competent authorities of the Member States concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member state, CMS: Germany) concerned the generic versions of irbesartan 75 mg, 150 mg and 300 mg film-coated tablets (Irbesartan Elpen film-coated tablets, named Irbesartan Aeno-rasis in Germany).

One bioequivalence study was submitted to support these applications comparing the applicant's test product with the reference product Aprovel 300 mg film-coated tablets (Sanofi Clir SNC), authorised for marketing since 1997.

With the exception of the bioequivalence study no new clinical or preclinical data, other than supporting literature, were submitted, which is acceptable for generic applications.

Based on the review of the data on quality, safety and efficacy, the Member States have granted marketing authorisation for Irbesartan Elpen 75 mg, 150 mg and 300 mg film-coated tablets from Elpen Pharmaceutical Co. Inc.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC as amended (generic application).

Irbesartan is a potent, orally active, selective angiotensin-II receptor (type AT1) antagonist.

The products are indicated in adults for the treatment of essential hypertension. They are also indicated for the 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 Summary of Product Characteristics (SmPC).

II. QUALITY ASPECTS

II.1 Introduction

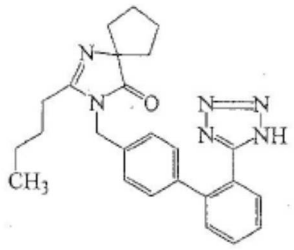
The chemical-pharmaceutical assessment report concerns the application of Irbesartan Elpen 75 mg, 150 mg and 300 mg film-coated tablets via a decentralized procedure according to Article 10(1) of Directive 2001/83/EC (i.e. a generic application). The products have been developed by Elpen Pharmaceutical Co. Inc.

The reference products were Aprovel 75 mg, 150 mg, 300 mg film-coated tablets (containing 75, 150 and 300 mg irbesartan, respectively as active ingredient), which were the original products of Sanofi Pharma Bristol-Myers Squibb SNC.

II.2 Drug substance

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the European Pharmacopoeia (Ph. Eur.) Certificate of Suitability (CEP) procedures with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: irbesartan
Chemical name: 2-Butyl-3-[p-(O-1H-tetrazol-5-yl-phenyl)benzyl]-1,3-diazaspiro-[4.4]non-1-en-4-one *or*
2-Butyl-3[(2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl]-1,3-diazaspiro-[4.4]non-1-en-4-one
Structure:



The active substance is white or almost white, crystalline powder, which is practically insoluble in water, sparingly soluble in methanol, slightly soluble in methylene chloride.

The substance is specified according to the requirements of the current Ph. Eur. monograph and the relevant CEP.

The Ph. Eur. specification includes the following tests for irbesartan: appearance, solubility, identification (by IR), appearance of solution, heavy metals, water, sulphated ash, impurity B, related substances and assay.

Testing methods are performed in accordance with the Ph. Eur. monograph and the annex of the current CEP on irbesartan. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised. The substance complies with the requirements of the European Medicines Agency (EMA) guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

A retest period has been justified by the submitted stability data. The quality of the primary packaging material is indicated on the CEP (two triple laminated bags placed in a polyethylene container).

Good Manufacturing Practice (GMP) compliance of the drug substance manufacture is demonstrated by the applicant.

II.3 Medicinal product

The aim of the pharmaceutical development was to develop a product essentially similar to the originator. The qualitative composition of the drug product is more or less the same as that of the reference product Aprovel film-coated tablets (Sanofi).

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards impurity profile, physico-chemical characteristics and dissolution profile, the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained.

Irbesartan Elpen 75 mg film-coated tablets are white and oval (10.5×5.5 mm).
Irbesartan Elpen 150 mg film-coated tablets are white and oval (13.5×7.0 mm).
Irbesartan Elpen 300 mg film-coated tablets are white and (17.0×9.0 mm).

The excipients used in the finished product are microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, silica colloidal anhydrous, magnesium stearate and hypromellose. The film-coating consists of polyvinyl alcohol (partially hydrolysed), macrogol/polyethylene glycol 3350, titanium dioxide (E171) (C.I. 77891) and talc.

All excipients used comply with their respective Ph. Eur. monographs except for the film-coating material, which is tested according to the manufacturer's specifications. Compliance of the

product with the general monograph of the Ph. Eur. on *the Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the International Council of Harmonisation (ICH) Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification.

The container closure system of the product is PVC/PVDC//Al blister or PVC/PVDC//Al perforated unit dose blister. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 3 years with the storage condition **"**Store below 25° C" is approved.

The SmPC, Patient Information (Package) Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

Irbesartan Elpen film-coated tablets are, from chemical-pharmaceutical aspects, approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of irbesartan are well known. Since irbesartan is a widely used, well-known active substance, no further studies are required and none have been provided. An overview based on literature review is, thus, appropriate. A non-clinical overview has been written by a qualified person and is satisfactory.

III.2 Pharmacology

Irbesartan is a potent, orally active, selective angiotensin-II receptor (type AT1) antagonist. It is expected to block all actions of angiotensin-II mediated by the AT1 receptor, regardless of the source or route of synthesis of angiotensin-II. The selective antagonism of the angiotensin-II (AT1) 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.

III.3 Pharmacokinetics

After oral administration, irbesartan is well absorbed. Concomitant food intake does not significantly influence the bioavailability of irbesartan. Plasma protein binding is high, with negligible binding to cellular blood components. Irbesartan is metabolised by the liver via glucuronide conjugation and oxidation. The major circulating metabolite is irbesartan glucuronide. In vitro studies indicate that irbesartan is primarily oxidised by the cytochrome P450 enzyme CYP2C9; isoenzyme CYP3A4 has negligible effect.

Irbesartan exhibits linear and dose proportional pharmacokinetics.

Irbesartan and its metabolites are eliminated by both biliary and renal pathways.

III.4 Toxicology

There was no evidence of abnormal systemic or target organ toxicity at clinically relevant doses. In non-clinical safety studies, high doses of irbesartan (≥ 250 mg/kg/day in rats and ≥ 100 mg/kg/day in macaques) caused a reduction of red blood cell parameters (erythrocytes, hemoglobin, hematocrit). At very high doses (≥ 500 mg/kg/day) degenerative changes in the kidney (such as interstitial nephritis, tubular distension, basophilic tubules, increased plasma concentrations of urea and creatinine) were induced by irbesartan in the rat and the macaque and are considered secondary to the hypotensive effects of the medicinal product which led to decreased

renal perfusion. Furthermore, irbesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells (in rats at ≥ 90 mg/kg/day, in macaques at ≥ 10 mg/kg/day). All of these changes were considered to be caused by the pharmacological action of irbesartan. For therapeutic doses of irbesartan in humans, the hyperplasia/ hypertrophy of the renal juxtaglomerular cells does not appear to have any relevance.

There was no evidence of mutagenicity, clastogenicity or carcinogenicity.

Fertility and reproductive performance were not affected in studies of male and female rats even at oral doses of irbesartan causing some parental toxicity (from 50 to 650 mg/kg/day), including mortality at the highest dose. No significant effects on the number of corpora lutea, implants, or live fetuses were observed. Irbesartan did not affect survival, development, or reproduction of offspring. Studies in animals indicate that the radiolabeled irbesartan is detected in rat and rabbit fetuses. Irbesartan is excreted in the milk of lactating rats.

Animal studies with irbesartan showed transient toxic effects (increased renal pelvic cavitation, hydroureter or subcutaneous oedema) in rat foetuses, which were resolved after birth. In rabbits, abortion or early resorption were noted at doses causing significant maternal toxicity, including mortality. No teratogenic effects were observed in the rat or rabbit.

III.5 Ecotoxicology/environmental risk assessment

Since Irbesartan Elpen is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Abridged applications avoid the need for repetitive tests on animals and humans.

No new non-clinical studies were conducted, which is acceptable for generic applications.

There are no objections to the approval of these applications from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of irbesartan are well known. With exception of data from the bioequivalence study below, no new clinical data are provided or are required for these applications. The clinical overview has been written by a qualified person and is satisfactory.

IV.2 Pharmacokinetics

IV.2.1 Literature data

After oral administration, irbesartan is well absorbed: studies of absolute bioavailability gave values of approximately 60-80%. Concomitant food intake does not significantly influence the bioavailability of irbesartan. Plasma protein binding is approximately 96%, with negligible binding to cellular blood components. The volume of distribution is 53 - 93 litres. Following oral or intravenous administration of 14C irbesartan, 80-85% of the circulating plasma radioactivity is attributable to unchanged irbesartan. Irbesartan is metabolised by the liver via glucuronide conjugation and oxidation. The major circulating metabolite is irbesartan glucuronide (approximately 6%). In vitro studies indicate that irbesartan is primarily oxidised by the cytochrome P450 enzyme CYP2C9; isoenzyme CYP3A4 has negligible effect.

Irbesartan exhibits linear and dose proportional pharmacokinetics over the dose range of 10 to 600 mg. A less than proportional increase in oral absorption at doses beyond 600 mg (twice the maximal recommended dose) was observed; the mechanism for this is unknown. Peak plasma concentrations are attained at 1.5 - 2 hours after oral administration. The total body and renal clearance are 157 - 176 and 3 - 3.5 ml/min, respectively. The terminal elimination half-life of irbesartan is 11 - 15 hours. Steady-state plasma concentrations are attained within 3 days after initiation of a once-daily dosing regimen. Limited accumulation of irbesartan (< 20%) is observed in plasma upon repeated once-daily dosing. In a study, somewhat higher plasma concentrations of irbesartan were observed in female hypertensive patients. However, there was no difference in the half-life and accumulation of irbesartan. No dosage adjustment is necessary in female patients. Irbesartan AUC and Cmax values were also somewhat greater in older subjects (≥ 65 years) than those of young subjects (18 - 40 years). However the terminal half-life was not significantly altered. No dosage adjustment is necessary in older people.

Irbesartan and its metabolites are eliminated by both biliary and renal pathways. After either oral or IV administration of ^{14}C irbesartan, about 20% of the radioactivity is recovered in the urine, and the remainder in the faeces. Less than 2% of the dose is excreted in the urine as unchanged irbesartan.

IV.2.2 Bioequivalence study

In support of these applications, the applicant submitted the following bioequivalence study.

Study design

It was a single dose, randomized, two-period, two-treatment, two-sequence, crossover, bioavailability study on Irbesartan 300 mg film-coated tablets (Test T, Elpen Pharmaceutical Co. Inc., Greece) versus Aprovel 300 mg film-coated tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France, Reference R) in healthy volunteers under fasting conditions.

In each study period each subject received either one single dose of test or reference study medications according to the randomization schedule under fasting conditions. The washout period between doses was adequate.

Determination of irbesartan in plasma samples was performed using a validated LC/MS/MS method.

Results of evaluation of bioequivalence criteria:

Parameter	Point Estimate T/R	Lower limit	Upper limit
$AUC_{(0-t)}$	96.24%	89.26%	103.77%
C_{max}	109.50%	100.03%	119.86%

AUC_{0-t}: area under the plasma concentration-time curve from administration to last observed concentration at time t.
C_{max}: maximum plasma concentration

Conclusion on the bioequivalence study

The results derived from the analysis of log-transformed primary efficacy pharmacokinetic parameters (Cmax, AUC(0-t) of irbesartan the Test/Reference ratios of group LS (least- squares) means and their 90% confidence intervals were included within the predefined acceptance interval of 80% - 125%.

Based on results of the bioequivalence study the Test product (Irbesartan Elpen 300 mg film-coated tablets, Elpen Pharmaceutical Co. Inc.) and the Reference product (Aprovel 300 mg film-coated tablets, Sanofi Pharma Bristol-Myers Squibb SNC) can be considered as bioequivalent in healthy adult subjects, under fasting condition.

Biowaiver for the lower strengths

As the lower strengths have fulfilled all the criteria for the biowaiver laid in the Guideline *on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1), the results and conclusions of the bioequivalence study can be extrapolated to the lower strengths.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none are required for applications of this type.

IV.4 Clinical efficacy

No new efficacy data were submitted and none are required for applications of this type.

IV.5 Clinical safety

No new safety data were submitted and none are required for applications of this type.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant Good Vigilance Practice module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

Summary of safety concerns	
Important identified risks	• Hypotension. • Dual blockade of the renin-angiotensin-aldosterone system (RAAS). • Hyperkalaemia. • Concomitant use with lithium. • Foetotoxicity and neonatal toxicity during the 2nd and 3rd trimester of pregnancy. • Impaired renal function including cases of renal failure.
Important potential risks	• Teratogenicity during the 1st trimester of pregnancy. • Use in patients with renovascular hypertension.

Summary of safety concerns	
	• Myocardial infarction or stroke. • Use in patients suffering from aortic, ortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy. • Concomitant use with non -steroidal anti-inflammatory drugs.
Missing information	• Use in patients with kidney transplantation. • Use in patients with severe hepatic impairment. • Use in paediatric population.

Pharmacovigilance Plan: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Irbesartan Elpen 75 mg, 150 mg and 300 mg film-coated tablets.

No additional activities are proposed.

Risk Minimisation Measures: routine risk minimisation measures (i.e. wording in SmPC, package leaflet and classification as a prescription-only medicine) are considered sufficient to manage all of the safety concerns connected to Irbesartan Elpen 75 mg, 150 mg and 300 mg film-coated tablets.

No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

IV.6.3 Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for these medicinal products are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

IV.7 Discussion on the clinical aspects

Abridged applications avoid the need for repetitive tests on animals and humans. For these application the bioequivalence studies described in section IV.2 are pivotal.

The present application contains an adequate review of published clinical data and the bioequivalence between Irbesartan Elpen 300 mg film-coated tablets and Aprovel 300 mg film-coated tablets has been demonstrated. As the lower strengths meet the biowaiver criteria specified in the Guideline *on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1), the results and conclusions of the bioequivalence study can be extrapolated to the 75 mg and 150 mg strengths.

Approval is recommended from the clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present application concerns Irbesartan Elpen 75 mg, 150 mg and 300 mg film-coated tablets, generic versions of irbesartan. The applicant and the future holder of authorisation in the RMS is Elpen Pharmaceutical Co. Inc.

The products are indicated in adults for the treatment of essential hypertension. They are also indicated for the treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive medicinal product regimen.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application). The reference product was Aprovel 300 mg film-coated tablets (Sanofi Pharma Bristol-Myers Squibb). As the lower strengths meet the biowaiver criteria, bioequivalence can be extended to the 75 mg and 150 mg tablets.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised.

The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Irbesartan Elpen 75 mg, 150 mg and 300 mg film-coated tablets.

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and user consultation

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 language used for the purpose of user testing the patient information leaflet was Hungarian.

The results show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

VI. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached