**Irbesartan 75 mg tablets**  
**Irbesartan 150 mg tablets**  
**Irbesartan 300 mg tablets**

**PL 06464/2687-9**

**UK Public Assessment Report**

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Irbesartan 75 mg, 150 mg and 300 mg tablets

PL 06464/2687-9

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Waymade Plc Marketing Authorisations (licences) for the medicinal products, Irbesartan 75 mg, 150 mg and 300 mg tablets (PL 06464/2687-9) on 08 August 2012. These are prescription-only medicines (POM).

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 prevents the binding of angiotensin-II to these receptors, causing the blood vessels to relax and the blood pressure to lower. Irbesartan also slows the decrease of kidney function in patients with high blood pressure and type 2 diabetes. Irbesartan tablets are used:

- 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

Based on the data submitted by Waymade Plc, Irbesartan 75 mg, 150 mg and 300 mg tablets were considered to be generic versions of the innovator products, Aprovel 75 mg, 150 mg and 300 mg film-coated tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France).

No new or unexpected safety concerns arose from these applications. It was judged that the benefits of Irbesartan 75 mg, 150 mg and 300 mg tablets outweigh the risks; hence Marketing Authorisations have been granted.
Irbesartan 75 mg, 150 mg and 300 mg tablets

PL 06464/2687-9

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Waymade Plc Marketing Authorisations for the medicinal products, Irbesartan 75 mg, 150 mg and 300 mg tablets (PL 06464/2687-9) on 08 August 2012. These are prescription-only medicines (POM).

These are generic applications for Irbesartan 75 mg, 150 mg and 300 mg tablets, submitted under Article 10(1) of Directive 2001/83 EC, as amended. The applications refer to the innovator products, Aprovel 75 mg, 150 mg and 300 mg film-coated tablets (EU/1/97/046/016, 021 and 026), authorised to Sanofi Pharma Bristol-Myers Squibb SNC, France, since 27 August 1997, via the centralised procedure. Aprovel 75 mg, 150 mg and 300 mg film-coated tablets have been authorised in the UK for more than 10 years, thus the period of data exclusivity has expired.

Irbesartan 75 mg, 150 mg and 300 mg tablets are indicated in adults for the treatment of:

- essential hypertension
- renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive medicinal product regimen (see section 5.1 of SmPC)

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. 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.

No new non-clinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years.

The applications are supported by a bioequivalence study comparing the pharmacokinetic profile of the test product, Irbesartan 150 mg tablets, to that of the reference product, Aprovel 150 mg film-coated tablets (Sanofi Pharma Bristol-Myers Squibb SNC, Germany). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

The MHRA considers that the pharmacovigilance system described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for
pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP). As the applications are for generic versions of already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active is well-established.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Irbesartan

Nomenclature:

INN: Irbesartan
Chemical name: 2-Butyl-3-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one

Structure:

![Structure of Irbesartan]

Molecular formula: C_{25}H_{28}N_{6}O
Molecular weight: 428.53 g/mol
CAS No: 138402-11-6
Physical form: White or almost white, crystalline powder
Solubility: Practically insoluble in water, slightly soluble in alcohol and in methylene chloride

The active substance, irbesartan, is the subject of a European Pharmacopoeia (Ph. Eur) monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

Appropriate specifications have been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specifications. Satisfactory Certificates of Analysis have been provided for reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary packaging in direct contact with the active substance complies with relevant Ph. Eur. requirements and satisfies Directive 2002/72/EC (as amended); it is suitable for contact with foodstuffs.
Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and an appropriate retest period has been applied.

FINISHED PRODUCT

Description and Composition

Irbesartan 75 mg, 150 mg and 300 mg tablets are presented as white to off-white, oval, film-coated tablets, debossed with “75”/“150”/“300” on one side and “J” on the other side. Each tablet contains 75 mg, 150 mg or 300 mg of the active ingredient, irbesartan.

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, colloidal anhydrous silica, microcrystalline cellulose, croscarmellose sodium, hypromellose, pregelatinised starch and magnesium stearate making up the tablet cores; and titanium dioxide (E171), macrogol 4000, lactose monohydrate and hypromellose constituting the film-coating. Appropriate justification for the inclusion of each excipient has been provided.

All excipients of the tablet cores comply with their respective Ph. Eur monographs. The film-coating formulation complies with satisfactory in-house specifications and its constituents comply with their respective Ph. Eur monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The only excipients used that contain material of animal or human origin are magnesium stearate and lactose monohydrate. A satisfactory TSE declaration has been provided for magnesium stearate, stating that it meets the criteria described in the current version of the monograph ‘Products with risk of transmitting agents of animal spongiform encephalopathies’. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used.

Pharmaceutical development

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The objective was to develop stable, generic, immediate-release, tablet formulations containing 75 mg, 150 mg and 300 mg of irbesartan, bioequivalent to the innovator products, Aprovel 75 mg, 150 mg and 300 mg film-coated tablets (Sanofi Pharma Bristol-Myers Squibb SNC).

Comparative dissolution data were provided for batches of the test and appropriate reference products. The dissolution profiles were satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.
In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies were conducted on pilot-scale batches and the results were satisfactory. The validation data demonstrated consistency of the manufacturing process. A commitment has been made by the MAH that full process validation will be conducted on commercial scale batches in accordance with the process validation protocol.

**Finished product specifications**

Finished product specifications are provided for release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

**Container Closure System**

Irbesartan 75 mg, 150 mg and 300 mg tablets are licensed for marketing in polyvinylchloride (PVC)/polyvinylidene chloride (PVdC)-aluminium foil blister strips, which are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 28, 56, 84 and 98 film-coated tablets. The MAH has stated that not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. These data support the applied shelf-life of 36 months. These medicinal products do not require any special storage conditions.

**Quality Overall Summary**

A satisfactory quality overall summary was provided and was prepared by an appropriately qualified expert. The CV of the expert has been supplied.

**Product Information**

The approved Summaries of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory. Mock-ups of the PIL and labelling have been provided. The labelling fulfils the statutory requirements for Braille.

The PIL is in line with the SmPC and is satisfactory. PIL user-testing has been accepted based on bridging to the successful user-testing of the ‘parent’ PIL for Irbesartan 75 mg, 150 mg and 300 mg film-coated tablets (Jubilant Pharmaceuticals nv, Belgium). The text, content and layout of the proposed PIL are considered to be sufficiently similar to the approved PIL for the stated product. The bridging is accepted.
The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the MHRA for approval before those packs are commercially marketed.

**Conclusion**

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. There are no objections to approval of Irbesartan 75 mg, 150 mg and 300 mg tablets from a pharmaceutical point of view.
NON-ClinICAL ASSESSMENT

These abridged applications, submitted under Article 10(1) of Directive 2001/83/EC, as amended, are for Irbesartan 75 mg, 150 mg and 300 mg tablets, products claiming to be generic versions of the centrally authorised innovator products, Aprovel 75 mg, 150 mg and 300 mg film-coated tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France).

No new non-clinical data have been supplied with these applications and none are required for applications of this type. A non-clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the expert has been supplied.

The MAH has provided adequate justification for not submitting a detailed Environmental Risk Assessment (ERA). These were applications for generic products and there is no reason to conclude that marketing of these products will change the overall use pattern of the existing market. There are no environmental concerns associated with the method of manufacture or formulation of the products.

There are no objections to approval of Irbesartan 75 mg, 150 mg and 300 mg tablets from a non-clinical point of view.
CLINICAL ASSESSMENT

BACKGROUND

Irbesartan is an Angiotensin II receptor antagonist. Angiotensin II receptor antagonists, also known as angiotensin receptor blockers (ARBs), AT1-receptor antagonists or sartans, are a group of pharmaceuticals which modulate the renin-angiotensin-aldosterone system. AT1-receptor antagonists block the activation of angiotensin II AT1-receptors. Blockade of AT1-receptors directly causes vasodilatation, reduces secretion of vasopressin, reduces production and secretion of aldosterone, amongst other actions – the combined effect of which is reduction of blood pressure. Their main use is in hypertension, diabetic nephropathy and congestive heart failure.

INDICATIONS

Irbesartan 75 mg, 150 mg and 300 mg tablets are indicated in adults for the treatment of:

- essential hypertension
- renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive medicinal product regimen (see section 5.1 of SmPC)

The indications are consistent with those for the innovator products and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

The usual recommended initial and maintenance dose is 150 mg once daily, with or without food. A dose of 150 mg once daily generally provides a better 24 hour blood pressure control than 75 mg. However, initiation of therapy with 75 mg could be considered, particularly in haemodialysed patients and in the elderly over 75 years. In patients insufficiently controlled with 150 mg once daily, the dose can be increased to 300 mg, or other antihypertensive agents can be added.

Full details concerning the posology are provided in the SmPCs. The posology is consistent with that for the innovator products and is satisfactory.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The clinical pharmacology of irbesartan is well-known. With the exception of the bioequivalence study, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for these applications.

Pharmacokinetics - Bioequivalence studies

The applications are supported by a bioequivalence study comparing the pharmacokinetic profile of the test product, Irbesartan 150 mg tablets, to that of the reference product, Aprovel 150 mg film-coated tablets (Sanofi Pharma Bristol-Myers Squibb SNC, Germany). The study was of an appropriate design and was conducted
to principles of Good Clinical Practice (GCP). Certificates of Analysis were provided for the test and reference products.

This was an open-label, randomised, two-period, two-sequence, two-treatment, single-dose crossover bioequivalence study conducted in healthy adult human male subjects under fasting conditions. Following an overnight fast of at least 10 hours, a single 150 mg dose of the investigational products was administered orally to each subject in each period. A satisfactory washout period of 10 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose and at specified time points up to 72.0 hours after administration of test or reference product. Plasma levels of irbesartan were quantified by a validated LC/MS-MS method.

The primary pharmacokinetic parameters for this study were $C_{\text{max}}$, $\text{AUC}_{0-t}$ and $\text{AUC}_{0-\infty}$. Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) of the ratio of the test and reference products fell within the acceptance range, 0.80-1.25 (80%-125%), for log-transformed $C_{\text{max}}$, $\text{AUC}_{0-t}$ and $\text{AUC}_{0-\infty}$ for irbesartan.

Results:
An appropriate number of subjects completed the study and were included in the pharmacokinetic evaluation and statistical analysis.

Safety - There were no deaths or serious or significant adverse events.

The summary of the results of the bioequivalence study are tabulated below:

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<th>Parameters</th>
<th>Geometric Least Squares Mean</th>
<th>90% CI (Parametric)</th>
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<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference product (X)</td>
<td>Test product (Y)</td>
<td>Ratio (Y/X)</td>
</tr>
<tr>
<td>2704.29</td>
<td>3051.50</td>
<td>112.84</td>
</tr>
<tr>
<td>$\text{AUC}_{0-t}$ (ng.h/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9404.86</td>
<td>9138.37</td>
<td>97.17</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty}$ (ng.h/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10380.61</td>
<td>10110.66</td>
<td>97.40</td>
</tr>
</tbody>
</table>

$C_{\text{max}}$ maximum plasma concentration  
$\text{AUC}_{0-t}$ area under the plasma concentration-time curve from time zero to t hours  
$\text{AUC}_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity

Conclusion on Bioequivalence
The results of the bioequivalence study show that the 150 mg strength test and reference products are bioequivalent, under fasting conditions, as the confidence intervals for $C_{\text{max}}$, $\text{AUC}_{0-t}$, and $\text{AUC}_{0-\infty}$ for irbesartan fall within the acceptance criteria ranges of 80-125%.
Satisfactory justification is provided for a bio-waiver for Irbesartan 75 mg and 300 mg tablets. As Irbesartan 75 mg, 150 mg and 300 mg tablets meet the criteria specified in the “Note for Guidance on the Investigation of Bioavailability and Bioequivalence” (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 150 mg strength can be extrapolated to the 75 mg and 300 mg strength tablets.

CLINICAL EFFICACY

No new data have been submitted and none are required. The reference products are established and the applications are supported by the demonstration of bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of irbesartan is well-established from its extensive use in clinical practice.

CLINICAL SAFETY

No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of irbesartan is well-known.

CLINICAL OVERVIEW

A satisfactory clinical overview was provided and was prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPCs are consistent with those of the innovator products and are acceptable.

Patient Information Leaflet

The final PIL is in line with the approved SmPCs and is satisfactory.

Labelling

The labelling is satisfactory.

CONCLUSIONS

Sufficient clinical information has been submitted to support these applications. The risk-benefit of the products is considered favourable from a clinical perspective. The grant of Marketing Authorisations was, therefore, recommended.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Irbesartan 75 mg, 150 mg and 300 mg tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Irbesartan 150 mg tablets and the reference product, Aprovel 150 mg film-coated tablets (Sanofi Pharma Bristol-Myers Squibb SNC, Germany).

As Irbesartan 75 mg, 150 mg and 300 mg tablets meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 150 mg strength were extrapolated to the 75 mg and 300 mg strength tablets, and omission of further bioequivalence studies on the other strengths can be accepted.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The approved SmPCs are consistent with those for the reference products and are satisfactory.

A mock-up PIL has been provided. The package leaflet is in line with the SmPCs and is satisfactory. PIL user-testing has been accepted based on bridging to the successful user-testing of the ‘parent’ PIL for Irbesartan 75 mg, 150 mg and 300 mg film-coated tablets (Jubilant Pharmaceuticals nv, Belgium). The results show that the 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.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label. The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the MHRA for approval before those packs are commercially marketed.

BENEFIT- RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant’s Irbesartan 75 mg, 150 mg and 300 mg tablets are generic versions of the reference products, Aprovel 75 mg, 150 mg and 300 mg film-coated
tablets (Sanofi Pharma Bristol-Myers Squibb SNC). Extensive clinical experience with irbesartan is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.
Irbesartan 75 mg, 150 mg and 300 mg tablets

PL 06464/2687-9

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the Marketing Authorisation applications on 15 May 2009.

2. Following standard checks and communication with the applicant the MHRA considered the applications valid on 11 June 2009.

3. Following assessment of the applications the MHRA requested further information relating to the clinical dossier on 06 November 2009; and further information relating to the quality dossier on 17 November 2009 and 14 March 2011.

4. The applicant responded to the MHRA’s requests, providing further information for the clinical sections on 14 June 2012; and further information for the quality sections on 12 January 2011 and 17 June 2011.

5. The applications were approved on 08 August 2012.
Irbesartan 75 mg, 150 mg and 300 mg tablets

PL 06464/2687-9

STEPS TAKEN AFTER AUTHORISATION

Not applicable
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Irbesartan 75 mg, 150 mg and 300 mg tablets (PL 06464/2687-9) is as follows. Differences between the individual SmPCs are highlighted:

1 NAME OF THE MEDICINAL PRODUCT

Irbesartan 75 mg tablets
Irbesartan 150 mg tablets
Irbesartan 300 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet Irbesartan 75/150/300 mg contains 75/150/300 mg irbesartan.

Excipient:
32/64/128 mg lactose monohydrate per tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, oval shaped, tablets debossed with “J” on one side and “75”/“150”/“300” on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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 (see section 5.1).

4.2 Posology and method of administration

Posology

The usual recommended initial and maintenance dose is 150 mg once daily, with or without food.

Irbesartan at a dose of 150 mg once daily generally provides a better 24 hour blood pressure control than 75 mg. However, initiation of therapy with 75 mg could be considered, particularly in haemodialysed patients and in the elderly over 75 years.

In patients insufficiently controlled with 150 mg once daily, the dose of Irbesartan can be increased to 300 mg, or other anti-hypertensive agents can be added. In particular, the addition of a diuretic such as hydrochlorothiazide has been shown to have an additive effect with Irbesartan (see section 4.5).

In hypertensive type 2 diabetic patients, therapy should be initiated at 150 mg irbesartan once daily and titrated up to 300 mg once daily as the preferred maintenance dose for treatment of renal disease.

The demonstration of renal benefit of Irbesartan in hypertensive type 2 diabetic patients is based on studies where irbesartan was used in addition to other antihypertensive agents, as needed, to reach target blood pressure (see section 5.1).
Special Populations

Renal impairment: no dosage adjustment is necessary in patients with impaired renal function. A lower starting dose (75 mg) should be considered for patients undergoing haemodialysis (see section 4.4).

Hepatic impairment: no dosage adjustment is necessary in patients with mild to moderate hepatic impairment. There is no clinical experience in patients with severe hepatic impairment.

Elderly patients: although consideration should be given to initiating therapy with 75 mg in patients over 75 years of age, dosage adjustment is not usually necessary for the elderly.

Paediatric patients: the safety and efficacy of Irbesartan in children aged 0 to 18 has not been established. Currently available data are described in section 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Method of Administration

For oral use.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients (see section 6.1).

Second and third trimester of pregnancy (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

Intravascular volume depletion: symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of Irbesartan.

Renovascular hypertension: there is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system. While this is not documented with Irbesartan, a similar effect should be anticipated with angiotensin-II receptor antagonists.

Renal impairment and kidney transplantation: when Irbesartan is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of Irbesartan in patients with a recent kidney transplantation.

Hypertensive patients with type 2 diabetes and renal disease: the effects of irbesartan both on renal and cardiovascular events were not uniform across all subgroups, in an analysis carried out in the study with patients with advanced renal disease. In particular, they appeared less favourable in women and non-white subjects (see section 5.1).

Hyperkalaemia: as with other medicinal products that affect the renin-angiotensin-aldosterone system, hyperkalaemia may occur during the treatment with Irbesartan, especially in the presence of renal impairment, overt proteinuria due to diabetic renal disease, and/or heart failure. Close monitoring of serum potassium in patients at risk is recommended (see section 4.5).

Lithium: the combination of lithium and Irbesartan is not recommended (see section 4.5).

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy: as with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.
Primary aldosteronism: patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of Irbesartan is not recommended.

General: in patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with angiotensin converting enzyme inhibitors or angiotensin-II receptor antagonists that affect this system has been associated with acute hypotension, azotaemia, oliguria, or rarely acute renal failure. As with any antihypertensive agent, excessive blood pressure decrease in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

As observed for angiotensin converting enzyme inhibitors, irbesartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population (see section 5.1).

Pregnancy: Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy.

Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Lactose: this medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Paediatric patients: irbesartan has been studied in paediatric populations aged 6 to 16 years old but the current data are insufficient to support an extension of the use in children until further data become available (see sections 4.8, 5.1 and 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

Diuretics and other antihypertensive agents: other antihypertensive agents may increase the hypotensive effects of irbesartan; however Irbesartan has been safely administered with other antihypertensive agents, such as beta-blockers, long-acting calcium channel blockers, and thiazide diuretics. Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with Irbesartan (see section 4.4).

Potassium supplements and potassium-sparing diuretics: based on experience with the use of other medicinal products that affect the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase serum potassium levels (e.g. heparin) may lead to increases in serum potassium and is, therefore, not recommended (see section 4.4).

Lithium: reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Similar effects have been very rarely reported with irbesartan so far. Therefore, this combination is not recommended (see section 4.4). If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Non-steroidal anti-inflammatory drugs: when angiotensin II antagonists are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.
As with ACE inhibitors, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Additional information on irbesartan interactions: in clinical studies, the pharmacokinetics of irbesartan is not affected by hydrochlorothiazide. Irbesartan is mainly metabolised by CYP2C9 and to a lesser extent by glucuronidation. No significant pharmacokinetic or pharmacodynamic interactions were observed when irbesartan was coadministered with warfarin, a medicinal product metabolised by CYP2C9. The effects of CYP2C9 inducers such as rifampicin on the pharmacokinetic of irbesartan have not been evaluated. The pharmacokinetic of digoxin was not altered by coadministration of irbesartan.

4.6 Pregnancy and lactation

Pregnancy:
The use of AIIRAs is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Antagonists (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to AIIRAs therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).

Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see sections 4.3 and 4.4).

Breast-feeding:
Because no information is available regarding the use of Irbesartan during breast-feeding, Irbesartan is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

It is unknown whether irbesartan or its metabolites are excreted in human milk.

Available pharmacodynamic/toxicological data in rats have shown excretion of irbesartan or its metabolites in milk (for details see 5.3).

Fertility
Irbesartan had no effect upon fertility of treated rats and their offspring up to the dose levels including the first signs of parental toxicity (see section 5.3).
4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Based on its pharmacodynamic properties, irbesartan is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that dizziness or weariness may occur during treatment.

4.8 Undesirable effects

In placebo-controlled trials in patients with hypertension, the overall incidence of adverse events did not differ between the irbesartan (56.2%) and the placebo groups (56.5%). Discontinuation due to any clinical or laboratory adverse event was less frequent for irbesartan-treated patients (3.3%) than for placebo-treated patients (4.5%). The incidence of adverse events was not related to dose (in the recommended dose range), gender, age, race, or duration of treatment.

In diabetic hypertensive patients with microalbuminuria and normal renal function, orthostatic dizziness and orthostatic hypotension were reported in 0.5% of the patients (i.e., uncommon) but in excess of placebo.

The following table presents the adverse drug reactions that were reported in placebo-controlled trials in which 1,965 hypertensive patients received irbesartan. Terms marked with a star (*) refer to the adverse reactions that were additionally reported in > 2% of diabetic hypertensive patients with chronic renal insufficiency and overt proteinuria and in excess of placebo.

The frequency of adverse reactions listed below is defined using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse reactions additionally reported from post–marketing experience are also listed. These adverse reactions are derived from spontaneous reports.

**Immune system disorders:**

Not known: hypersensitivity reactions such as angioedema, rash, urticaria

**Metabolism and nutrition disorders:**

Not known: hyperkalaemia

**Nervous system disorders:**

Common: dizziness, orthostatic dizziness*

Not known: vertigo, headache

**Ear and labyrinth disorder:**

Not known: tinnitus

**Cardiac disorders:**

Uncommon: tachycardia

**Vascular disorders:**

Common: orthostatic hypotension*

Uncommon: flushing

**Respiratory, thoracic and mediastinal disorders:**

Uncommon: cough

**Gastrointestinal disorders:**

Common: nausea/vomiting

Uncommon: diarrhoea, dyspepsia/heartburn

Not known: dysgeusia
**Hepatobiliary disorders:**
- Uncommon: jaundice
- Not known: hepatitis, abnormal liver function

**Skin and subcutaneous tissue disorders:**
- Not known: leukocytoclastic vasculitis

**Musculoskeletal and connective tissue disorders:**
- Common: musculoskeletal pain*
- Not known: arthralgia, myalgia (in some cases associated with increased plasma creatine kinase levels), muscle cramps

**Renal and urinary disorders:**
- Not known: impaired renal function including cases of renal failure in patients at risk (see section 4.4)

**Reproductive system and breast disorders:**
- Uncommon: sexual dysfunction

**General disorders and administration site conditions:**
- Common: fatigue
- Uncommon: chest pain

**Investigations:**

Very common: Hyperkalaemia* occurred more often in diabetic patients treated with irbesartan than with placebo. In diabetic hypertensive patients with microalbuminuria and normal renal function, hyperkalaemia (≥ 5.5 mEq/L) occurred in 29.4% of the patients in the irbesartan 300 mg group and 22% of the patients in the placebo group. In diabetic hypertensive patients with chronic renal insufficiency and overt proteinuria, hyperkalaemia (≥ 5.5 mEq/L) occurred in 46.3% of the patients in the irbesartan group and 26.3% of the patients in the placebo group.

Common: significant increases in plasma creatine kinase were commonly observed (1.7%) in irbesartan treated subjects. None of these increases were associated with identifiable clinical musculoskeletal events.

In 1.7% of hypertensive patients with advanced diabetic renal disease treated with irbesartan, a decrease in haemoglobin*, which was not clinically significant, has been observed.

Paediatric patients: in a randomised trial of 318 hypertensive children and adolescents aged 6 to 16 years, the following related adverse events occurred in the 3-week double-blind phase: headache (7.9%), hypotension (2.2%), dizziness (1.9%), cough (0.9%). In the 26-week open-label period of this trial the most frequent laboratory abnormalities observed were creatinine increases (6.5%) and elevated CK values in 2% of child recipients.

### 4.9 Overdose

Experience in adults exposed to doses of up to 900 mg/day for 8 weeks revealed no toxicity. The most likely manifestations of overdose are expected to be hypotension and tachycardia; bradycardia might also occur from overdose. No specific information is available on the treatment of overdose with Irbesartan. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Suggested measures include induction of emesis and/or gastric lavage. Activated charcoal may be useful in the treatment of overdose. Irbesartan is not removed by haemodialysis.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin-II antagonists, plain.
ATC code: C09CA04.

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

Mechanism of action: 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.

Clinical efficacy:

Hypertension

Irbesartan lowers blood pressure with minimal change in heart rate. The decrease in blood pressure is dose-related for once a day doses with a tendency towards plateau at doses above 300 mg. Doses of 150-300 mg once daily lower supine or seated blood pressures at trough (i.e. 24 hours after dosing) by an average of 8-13/5-8 mm Hg (systolic/diastolic) greater than those associated with placebo.

Peak reduction of blood pressure is achieved within 3-6 hours after administration and the blood pressure lowering effect is maintained for at least 24 hours. At 24 hours the reduction of blood pressure was 60-70% of the corresponding peak diastolic and systolic responses at the recommended doses. Once daily dosing with 150 mg produced trough and mean 24 hour responses similar to twice daily dosing on the same total dose.

The blood pressure lowering effect of Irbesartan is evident within 1-2 weeks, with the maximal effect occurring by 4-6 weeks after start of therapy. The antihypertensive effects are maintained during long term therapy. After withdrawal of therapy, blood pressure gradually returns toward baseline.

Rebound hypertension has not been observed.

The blood pressure lowering effects of irbesartan and thiazide-type diuretics are additive. In patients not adequately controlled by irbesartan alone, the addition of a low dose of hydrochlorothiazide (12.5 mg) to irbesartan once daily results in a further placebo-adjusted blood pressure reduction at trough of 7-10/3-6 mm Hg (systolic/diastolic).

The efficacy of Irbesartan is not influenced by age or gender. As is the case with other medicinal products that affect the renin-angiotensin system, black hypertensive patients have notably less response to irbesartan monotherapy. When irbesartan is administered concomitantly with a low dose of hydrochlorothiazide (e.g. 12.5 mg daily), the antihypertensive response in black patients approaches that of white patients.

There is no clinically important effect on serum uric acid or urinary uric acid secretion.

Paediatric population

Reduction of blood pressure with 0.5 mg/kg (low), 1.5 mg/kg (medium) and 4.5 mg/kg (high) target titrated doses of irbesartan was evaluated in 318 hypertensive or at risk (diabetic, family history of hypertension) children and adolescents aged 6 to 16 years over a three week period. At the end of the three weeks the mean reduction from baseline in the primary efficacy variable, trough seated systolic blood pressure (SeSBP) was 11.7 mmHg (low dose), 9.3 mmHg (medium dose), 13.2 mmHg (high dose). No significant difference was apparent between these doses. Adjusted mean change of trough seated diastolic blood pressure (SeDBP) was as follows: 3.8 mmHg (low dose), 3.2 mmHg (medium dose), 5.6 mmHg (high dose). Over a subsequent two week period where patients were re-randomized to either active medicinal product or placebo, patients on placebo had increases of 2.4 and 2.0 mmHg in
SeSBP and SeDBP compared to +0.1 and -0.3 mmHg changes respectively in those on all doses of irbesartan (see section 4.2).

Hypertension and type 2 diabetes with renal disease

The “Irbesartan Diabetic Nephropathy Trial (IDNT)” shows that irbesartan decreases the progression of renal disease in patients with chronic renal insufficiency and overt proteinuria. IDNT was a double blind, controlled, morbidity and mortality trial comparing Irbesartan, amlodipine and placebo. In 1,715 hypertensive patients with type 2 diabetes, proteinuria ≥ 900 mg/day and serum creatinine ranging from 1.0-3.0 mg/dl, the long-term effects (mean 2.6 years) of Irbesartan on the progression of renal disease and all-cause mortality were examined. Patients were titrated from 75 mg to a maintenance dose of 300 mg Irbesartan, from 2.5 mg to 10 mg amlodipine, or placebo as tolerated. Patients in all treatment groups typically received between 2 and 4 antihypertensive agents (e.g., diuretics, beta blockers, alpha blockers) to reach a predefined blood pressure goal of ≤ 135/85 mmHg or a 10 mmHg reduction in systolic pressure if baseline was > 160 mmHg. Sixty per cent (60%) of patients in the placebo group reached this target blood pressure whereas this figure was 76% and 78% in the irbesartan and amlodipine groups respectively. Irbesartan significantly reduced the relative risk in the primary combined endpoint of doubling serum creatinine, end-stage renal disease (ESRD) or all-cause mortality. Approximately 33% of patients in the irbesartan group reached the primary renal composite endpoint compared to 39% and 41% in the placebo and amlodipine groups [20% relative risk reduction versus placebo (p = 0.024) and 23% relative risk reduction compared to amlodipine (p = 0.006)]. When the individual components of the primary endpoint were analysed, no effect in all cause mortality was observed, while a positive trend in the reduction in ESRD and a significant reduction in doubling of serum creatinine were observed.

Subgroups consisting of gender, race, age, duration of diabetes, baseline blood pressure, serum creatinine, and albumin excretion rate were assessed for treatment effect. In the female and black subgroups which represented 32% and 26% of the overall study population respectively, a renal benefit was not evident, although the confidence intervals do not exclude it. As for the secondary endpoint of fatal and non-fatal cardiovascular events, there was no difference among the three groups in the overall population, although an increased incidence of non-fatal MI was seen for women and a decreased incidence of non-fatal MI was seen in males in the irbesartan group versus the placebo based regimen. An increased incidence of non-fatal MI and stroke was seen in females in the irbesartan-based regimen versus the amlodipine-based regimen, while hospitalization due to heart failure was reduced in the overall population. However, no proper explanation for these findings in women has been identified.

The study of the “Effects of Irbesartan on Microalbuminuria in Hypertensive Patients with type 2 Diabetes Mellitus (IRMA 2)” shows that irbesartan 300 mg delays progression to overt proteinuria in patients with microalbuminuria. IRMA 2 was a placebo-controlled double blind morbidity study in 590 patients with type 2 diabetes, microalbuminuria (30-300 mg/day) and normal renal function (serum creatinine ≤ 1.5 mg/dl in males and < 1.1 mg/dl in females). The study examined the long-term effects (2 years) of Irbesartan on the progression to clinical (overt) proteinuria (urinary albumin excretion rate (UAER) > 300 mg/day, and an increase in UAER of at least 30% from baseline). The predefined blood pressure goal was ≤ 135/85 mmHg. Additional antihypertensive agents (excluding ACE inhibitors, angiotensin II receptor antagonists and dihydropyridine calcium blockers) were added as needed to help achieve the blood pressure goal. While similar blood pressure was achieved in all treatment groups, fewer subjects in the irbesartan 300 mg group (5.2%) than in the placebo (14.9%) or in the irbesartan 150 mg group (9.7%) reached the endpoint of overt proteinuria, demonstrating a 70% relative risk reduction versus placebo (p = 0.0004) for the higher dose. An accompanying improvement in the glomerular filtration rate (GFR) was not observed during the first three months of treatment. The slowing in the progression to clinical proteinuria was evident as early as three months and continued over the 2 year period. Regression to normoalbuminuria (< 30 mg/day) was more frequent in the Irbesartan 300 mg group (34%) than in the placebo group (21%).
5.2 Pharmacokinetic properties

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 elderly 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 elderly patients.

Irbesartan and its metabolites are eliminated by both biliary and renal pathways. After either oral or IV administration of 14C 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.

Paediatric population

The pharmacokinetics of irbesartan were evaluated in 23 hypertensive children after the administration of single and multiple daily doses of irbesartan (2 mg/kg) up to a maximum daily dose of 150 mg for four weeks. Of those 23 children, 21 were evaluable for comparison of pharmacokinetics with adults (twelve children over 12 years, nine children between 6 and 12 years). Results showed that Cmax, AUC and clearance rates were comparable to those observed in adult patients receiving 150 mg irbesartan daily. A limited accumulation of irbesartan (18%) in plasma was observed upon repeated once daily dosing.

Renal impairment: in patients with renal impairment or those undergoing haemodialysis, the pharmacokinetic parameters of irbesartan are not significantly altered. Irbesartan is not removed by haemodialysis.

Hepatic impairment: in patients with mild to moderate cirrhosis, the pharmacokinetic parameters of irbesartan are not significantly altered.

Studies have not been performed in patients with severe hepatic impairment.

5.3 Preclinical safety data

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, haemoglobin, haematocrit).
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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

**Tablet core:**
- Lactose monohydrate
- Colloidal anhydrous silica
- Microcrystalline cellulose
- Croscarmellose sodium
- Hypromellose
- Pregelatinised starch
- Magnesium stearate

**Film-coating:**
- Titanium dioxide (E171)
- Macrogol 4000
- Lactose monohydrate
- Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

No special storage conditions.

6.5 Nature and contents of container

- 28 film-coated tablets
- 56 film-coated tablets
- 84 film-coated tablets
- 98 film-coated tablets

PVC/PVDC/Aluminium blisters
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Waymade Plc
Trading as: Sovereign Medical
Sovereign House
Miles Gray Road
Basildon
Essex
SS14 3FR
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 06464/2687
PL 06464/2688
PL 06464/2689

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/08/2012

10 DATE OF REVISION OF THE TEXT

08/08/2012
UKPAR Irbesartan 75 mg, 150 mg and 300 mg tablets

PL 06464/2687-9

PATIENT INFORMATION LEAFLET

SOVEREIGN MEDICAL

PACKAGE LEAFLET: INFORMATION FOR THE USER

Irbesartan 75 mg tablets
Irbesartan 150 mg tablets
Irbesartan 300 mg tablets
(brand name)

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects becomes severe, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Irbesartan is and what it is used for
2. Before you take Irbesartan
3. How to take Irbesartan
4. Possible side effects
5. How to store Irbesartan
6. Further information

1. WHAT IRESARTAN IS AND WHAT IT IS USED FOR

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 prevents the binding of angiotensin-II to these receptors, causing the blood vessels to relax and the blood pressure to lower.

Irbesartan slows the decrease of kidney function in patients with high blood pressure and type 2 diabetes.

Irbesartan is used
- 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.

2. BEFORE YOU TAKE IRBESARTAN

Do not take Irbesartan
- if you are allergic (hypersensitive) to Irbesartan or any other ingredients of Irbesartan tablets
- if you are more than 3 months pregnant. (It is also better to avoid Irbesartan in early pregnancy – see pregnancy section)

Irbesartan should not be given to children and adolescents (under 18 years).

Take special care with Irbesartan
Tell your doctor if any of the following apply to you:
- if you get excessive vomiting or diarrhoea;
- if you suffer from kidney problems;
- if you suffer from heart problems;
- if you receive Irbesartan for diabetic kidney disease. In this case your doctor may perform regular blood tests, especially for measuring blood potassium levels in case of poor kidney function;
- if you are going to have an operation (surgery) or be given anaesthetics.

You must tell your doctor if you think you are (or might become) pregnant. Irbesartan is not recommended in early pregnancy and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby at that stage (see pregnancy section).

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Irbesartan does not usually interact with other medicines.

You may need to have blood checks if you take:
- potassium supplements
- salt substitutes containing potassium
- potassium-sparing medicines (such as diuretics)
UKPAR Irbesartan 75 mg, 150 mg and 300 mg tablets

- medicines containing lithium
  If you take certain painkillers, called non-steroidal anti-inflammatory drugs, the effect of irbesartan may be reduced.

**Taking Irbesartan with food and drink**
Irbesartan can be taken with or without food.

**Pregnancy and breast-feeding**

**Pregnancy**
You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking irbesartan before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of irbesartan. Irbesartan is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

**Breast-feeding**
Tell your doctor if you are breast-feeding or about to start breast-feeding. Irbesartan is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, 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 is unlikely to affect your ability to drive or use machines. However, occasionally dizziness or weariness may occur during treatment of high blood pressure. If you experience these, talk to your doctor before attempting to drive or use machines.

**Important information about some of the ingredients of Irbesartan**
Irbesartan contains lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. **HOW TO TAKE IRBESARTAN**

Always take irbesartan exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

**Method of administration**
Irbesartan is for oral use. Swallow the tablets with a sufficient amount of fluid (e.g. one glass of water). You can take irbesartan with or without food. Try to take your daily dose at about the same time each day. It is important that you continue to take irbesartan until your doctor tells you otherwise.

- **Patients with high blood pressure**
The usual dose is 150 mg once a day. The dose may later be increased to 300 mg 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 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.

**If you take more Irbesartan than you should**
If you accidentally take too many tablets, contact your doctor immediately.

**Children should not take Irbesartan**
Irbesartan should not be given to children under 16 years of age. If a child swallows some tablets, contact your doctor immediately.

**If you forget to take Irbesartan**
If you accidentally miss a daily dose, just take the next dose as normal. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this product ask your doctor or pharmacist.

4. **POSSIBLE SIDE EFFECTS**

Like all medicines, irbesartan can cause side effects, although not everybody gets 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 you get any of these symptoms or get short of breath, stop taking Irbesartan and contact your doctor immediately.
The frequency of the side effects listed below is defined using the following convention:

Very common: at least 1 in 10 patients or more
Common: at least 1 in 100 and less than 1 in 10 patients
Uncommon: at least 1 in 1000 and less than 1 in 100 patients

Side effects reported in clinical studies for patients treated with irbesartan were:

- Very common: if you suffer from high blood pressure and type 2 diabetes with kidney disease, blood tests may show an increased level of potassium.

- Common: dizziness, feeling sick/vomiting, fatigue and blood tests may show raised levels of an enzyme that measures the muscle and heart function (creatinine 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: increased heart rate, flushing, cough, diarrhoea, indigestion/heartburn, sexual dysfunction (problems with sexual performance), chest pain.

Some undesirable effects have been reported since marketing of irbesartan but the frequency for them to occur is not known. These undesirable effects are: 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).

If any of the side effects becomes severe, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE IRBESARTAN

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

Do not use irbesartan after the expiry date which is stated on the carton and on the blister after EXP. The expiry date refers to the last day of that month.

No special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What irbesartan contains
- The active substance is irbesartan.
  - Each irbesartan 75 mg tablet contains 75 mg irbesartan.
  - Each irbesartan 150 mg tablet contains 150 mg irbesartan.
  - Each irbesartan 300 mg tablet contains 300 mg irbesartan.

- The other ingredients are lactose monohydrate, colloidal anhydrous silica, microcrystalline cellulose, croscarmellose sodium, hypromellose, pregelatinized starch, magnesium stearate, titanium dioxide (E171) and macrogol 4000.

What irbesartan looks like and contents of the pack
- Irbesartan 75 mg tablets are white to off-white, oval shaped, tablets debossed with “J” on one side and “75” on the other.
- Irbesartan 150 mg tablets are white to off-white, oval shaped, tablets debossed with “J” on one side and “150” on the other.
- Irbesartan 300 mg tablets are white to off-white, oval shaped, tablets debossed with “J” on one side and “300” on the other.

Irbesartan film-coated tablets are supplied in blister packs of 28, 56, 84 or 98 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder:
Waymade Plc
Trading as: Sovereign Medical
Sovereign House
Miles Gray Road
Basildon
Essex
SS14 3FR
United Kingdom

Manufacturer:
PSI supply nv
Axxes Business Park
Gurdensporenpark 22 – Block C
9820 Merelbeke
Belgium

Waymade Plc
Sovereign House
Miles Gray Road
Basildon
Essex
SS14 3FR
United Kingdom

This leaflet was last approved in April 2012.
LABELLING

Irbesartan 75 mg tablets - PL 06464/2687

Carton
Braille

irbesartan

(No.) 75 mg

tablets

Blister foil