IRBESARTAN 75, 150 AND 300MG FILM-COATED TABLETS

PL 24668/0106-8

UKPAR

TABLE OF CONTENTS

Lay Summary Page 2
Scientific discussion Page 3
Steps taken for assessment Page 12
Steps taken after authorisation – summary Page 13
Summary of Product Characteristics
Product Information Leaflet
Labelling
IRBESARTAN 75, 150 AND 300MG FILM-COATED TABLETS

PL 24668/0106-8

LAY SUMMARY

On the 4th April 2011 the MHRA granted Caduceus Pharma Limited Marketing Authorisations (licences) for the medicinal products Irbesartan 75, 150 and 300mg Film-coated Tablets. These medicines are only available on prescription from your doctor.

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 increased in blood pressure. Irbesartan prevents the binding of angiotensin-II to these receptors, causing the blood 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:
- in the treatment of high blood pressure (hypertension)
- to protect the kidney in patients with high blood pressure, type 2 diabetes and known impaired kidney function.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Irbesartan 75, 150 and 300mg Film-coated Tablets outweigh the risks. Hence, Marketing Authorisations have been granted.
IRBESARTAN 75, 150 AND 300MG FILM-COATED TABLETS

PL 24668/0106-8

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction Page 4
Pharmaceutical assessment Page 5
Preclinical assessment Page 8
Clinical assessment (including statistical assessment) Page 9
Overall conclusions and risk benefit assessment Page 11
INTRODUCTION

The MHRA granted Marketing Authorisations for the medicinal products Irbesartan 75, 150 and 300mg Film-coated Tablets (PL 24668/0106-8) on the 4th April 2011. These medicines are only available on prescription from your doctor.

Irbesartan 75, 150 and 300mg Film-coated Tablets are indicated for the Treatment of essential hypertension and renal disease in patients with hypertension and type 2 diabetes mellitus as part of the antihypertensive treatment regimen.

These are national abridged applications for Irbesartan 75, 150 and 300mg Film-coated Tablets submitted under article 10.1 of Directive 2001/83/EC, as amended. These products are cross-referring to Aprovel 75, 150 and 300mg Film-coated tablets (EM 16385/0001-3), authorised on 27th August 1997 to Sanofi Pharma Bristol Myers Squibb.

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 vasodilation, reduces secretion of vasopressin, reduces production and secretion of aldosterone, amongst other actions – the combined effect of which is reduction of blood pressure.

Details of a pharmacovigilance system have been provided with these applications and are satisfactory. A suitable justification for non-submission of the Risk Management Plan has been provided.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nomenclature
rINN: Irbesartan

Chemical Name:
- 2-butyl-3-[p-(O-1H-tetrazol-5-yl-phenyl)benzyl]-1,3-diazaspiro-[4.4]non-1-en-one;
- 1,3-Diazaspiro[4.4]non—1-en-4-one,
- 2-butyl-3-[[2’-(1H-tetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-

Structure:

Molecular Formula: C$_{25}$H$_{28}$N$_6$O
Molecular Weight: 428.5
Appearance: white to off-white crystalline powder.
Solubility: It is slightly soluble in ethanol (96 %), chloroform and methylene chloride and practically insoluble in water. It is also freely soluble in dilute alkaline solutions.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.
DRUG PRODUCT

Other ingredients
Other ingredients consist of the pharmaceutical excipients croscarmellose sodium, microcrystalline cellulose, hypromellose, mannitol, magnesium stearate non-bovine, silica, colloidal anhydrous making up the tablet core; and Opadry white (hydroxypropyl cellulose, hypromellose, polyethylene glycol and titanium dioxide) comprising the film-coating.

All excipients used comply with their respective European Pharmacopoeia monograph with the exception of Opadry white which complies with an in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has stated that none of the excipients are of animal or human origin and confirms that the magnesium stearate used is of vegetable origin.

Pharmaceutical development
Suitable pharmaceutical development data have been provided for these applications. Comparable dissolution and impurity profile are provided for these products versus the originator products.

Manufacture
A satisfactory batch formula has been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on pilot-scale batches have been provided. The results are satisfactory. The applicant has committed to perform process validation on future production full-scale batches before marketing the product.

Finished product specification
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System
The tablets are packed in Blister packs (Al/PVDC blisters) and Tablet containers (HDPE) with desiccant and LDPE cap. The pack sizes are 14, 28, 30, 56, 84, 90 and 98 tablets for blister and tablet container.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 24 months with no special storage condition is set and this is acceptable.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Form
The MAA forms are satisfactory.

Expert Report
The pharmaceutical expert report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of these products from a pharmaceutical point of view.
PRECLINICAL ASSESSMENT

The pharmacodynamic, pharmacokinetic and toxicological properties of irbesartan are well-known. Thus, the applicant has not provided additional studies and further studies are not required.

A preclinical expert report has been provided, written by an appropriately qualified person. This is satisfactory.

A suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of these products from a preclinical point of view.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

BIOEQUIVALENCE

A randomised, open label, two treatment, two sequence, single dose, crossover, bioequivalence study of Irbesartan 300 mg Film coated tablets (test) and Aprovel 300 mg Film-coated tablets in healthy adult subjects, under fasting conditions.

Blood samples were collected pre-dose and at 0.166, 0.333, 0.5, 0.75, 1.0, 1.333, 1.667, 2.0, 2.333, 2.667, 3.0, 3.333, 3.667, 4.0, 5.0, 6.0, 8.0, 12.0, 24.0, 36.0, 48.0 and 72.0 hours post-dose. The washout period was 11 days.

Results

Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals:

<table>
<thead>
<tr>
<th></th>
<th>Parent drug (T/R)</th>
<th>Active metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>107 (98-116%)</td>
<td>NA</td>
</tr>
<tr>
<td>$AUC_t$ (ng.h/mL)</td>
<td>99.9 (92-107%)</td>
<td>NA</td>
</tr>
<tr>
<td>$AUC_{\infty}$ (ng.h/mL)</td>
<td>100 (92-108%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

The results show that the 90% confidence intervals for $AUC$ ratios (both $0-t$ and $0-\infty$) and $C_{\text{max}}$ all fell within the acceptable range (80-125%). Bioequivalence has been demonstrated between the test formulation (Irbesartan 300 mg Film coated tablets) and the reference formulation (Aprovel 300 mg Film-coated tablets). Satisfactory justification is provided for a bio-waiver according to the Committee for Proprietary Medicinal Products Notes for Guidance on “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1 Corr**). The results of the study for 300mg formulation can therefore be extrapolated to the other strengths i.e 75mg and 150mg Film-coated Tablets.

EFFICACY

No new efficacy data have been submitted and none are required for this application.

SAFETY

No new safety data have been submitted and none are required for this application.

EXPERT REPORT

The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

SUMMARY OF PRODUCT CHARACTERISTICS

These are satisfactory.

PATIENT INFORMATION LEAFLET

This is satisfactory.
LABELLING
These are satisfactory.

MARKETING AUTHORISATION FORMS
These are satisfactory.

CONCLUSIONS
The Applicant has demonstrated that the products and the reference compounds are bioequivalent.

There are no objections to the approval of these products from a clinical point of view.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Irbesartan 75, 150 and 300mg Film-coated 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.

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

EFFICACY
No new data have been submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s Irbesartan 300 mg film coated tablets and the reference product, Aprovel 300 mg Film-coated tablets.

No new or unexpected safety concerns arise from these applications.

The SmPC and PIL are satisfactory and consistent with those for the reference products. Satisfactory labelling has also been submitted.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with irbesartan is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
## STEPS TAKEN FOR ASSESSMENT

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 11(^{\text{th}}) March 2009</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 20(^{\text{th}}) March 2009</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information relating to the quality dossier on 6(^{\text{th}}) November 2009, 8(^{\text{th}}) September 2010, 15(^{\text{th}}) December 2010 and on the clinical section on the 23(^{\text{rd}}) October 2009</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information to the quality section on 16(^{\text{th}}) June 2010, 17(^{\text{th}}) November 2010 and 28(^{\text{th}}) January 2011 and on the clinical section 12(^{\text{th}}) May 2010</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 4(^{\text{th}}) April 2011</td>
</tr>
</tbody>
</table>
IRBESARTAN 75, 150 AND 300MG FILM-COATED TABLETS

PL 24668/0106-8

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

13
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Irbesartan 75 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 75 mg irbesartan.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

The 75 mg tablets are white, elliptical, biconvex, film-coated, with diameter of 5.2 x 10 mm, marked 'I' on one side and '75' on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of essential hypertension.
Treatment of renal disease in 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
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).

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: irbesartan is not recommended for use in children and adolescents due to insufficient data on safety and efficacy (see sections 5.1 and 5.2).

4.3 Contraindications
Hypersensitivity to the active substance 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 drugs 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).

**Hyperkalemia:** as with other drugs that affect the renin-angiotensin-aldosterone system, hyperkalemia 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 anti-hypertensive 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 4.4 and 4.6).
**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

#### Inadvisable combinations

**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 pharmacokinetic 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 drug 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 trimesters 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 AIIRA 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 also sections 4.3 and 4.4)

**Lactation:** Because no information is available regarding the use of irbesartan during breastfeeding, irbesartan is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a new born or preterm infant.

### 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.

**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.
Cardiac disorders:
Uncommon: tachycardia

Nervous system disorders:
Common: dizziness, orthostatic dizziness*

Respiratory, thoracic and mediastinal disorders:
Uncommon: cough

Gastrointestinal disorders:
Common: nausea/vomiting
Uncommon: diarrhoea, dyspepsia/heartburn

Musculoskeletal and connective tissue disorders:
Common: musculoskeletal pain*

Vascular disorders:
Common: orthostatic hypotension*
Uncommon: flushing

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

Reproductive system and breast disorders:
Uncommon: sexual dysfunction

The following additional adverse reactions have been reported during post-marketing experience; they are derived from spontaneous reports and therefore, the frequency of these adverse reactions is not known:

Nervous system disorders:
Headache

Ear and labyrinth disorders:
Tinnitus

Gastrointestinal disorders:
Dysgeusia

Renal and urinary disorders:
Impaired renal function including cases of renal failure in patients at risk (see section 4.4)

Skin and subcutaneous tissue disorders:
Leukocytoclastic vasculitis

Musculoskeletal and connective tissue disorders:
Arthralgia, myalgia (in some cases associated with increased plasma creatine kinase levels), muscle cramps

Metabolism and nutrition disorders:
Hyperkalemia

Immune system disorders:
Hypersensitivity reactions such as angioedema, rash, urticaria

Hepato-biliary disorders:
Hepatitis, abnormal liver function
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 overdosage are expected to be hypotension and tachycardia; bradycardia might also occur from overdose. No specific information is available on the treatment of overdosage 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 C09C A04.

Mechanism of action: 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.

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.
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 \(^{14}\text{C}\) 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 \(^{14}\text{C}\) 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.

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.

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:
- Croscarmellose sodium
- Microcrystalline Cellulose
- Hypromellose
- Mannitol
- Magnesium stearate, non-bovine
- Silica, colloidal anhydrous

Tablet coating:
- Hydroxypropyl cellulose
- Hypromellose
- Polyethylene glycol
- Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister packs (Al/PVDC blisters)
Tablet containers (HDPE) with desiccant and LDPE cap

Pack sizes:

- Blisters:
  - Irbesartan 75 mg film-coated tablets: 14, 28, 30, 56, 84, 90, 98 tablets

- Tablet containers:
  - Irbesartan 75 mg film-coated tablets: 14, 28, 30, 56, 84, 90, 98 tablets

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
Caduceus Pharma Limited
6th floor
94 Wigmore Street
London
W1U 3 RF

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0106

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
04/04/2011

10 DATE OF REVISION OF THE TEXT
04/04/2011
1 NAME OF THE MEDICINAL PRODUCT
Irbesartan 150 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 150 mg irbesartan.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

The 150 mg tablets are white, elliptical, biconvex, film-coated, with diameter of 6.5 x 12.7 mm, marked ‘I’ on one side and ‘150’ on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of essential hypertension.
Treatment of renal disease in 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
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).

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: irbesartan is not recommended for use in children and adolescents due to insufficient data on safety and efficacy (see sections 5.1 and 5.2).

4.3 Contraindications
Hypersensitivity to the active substance 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 drugs 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).

**Hyperkalemia:** as with other drugs that affect the renin-angiotensin-aldosterone system, hyperkalemia 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 anti-hypertensive 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 4.4 and 4.6).
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

Inadvisable combinations

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 pharmacokinetic 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 drug 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 trimesters 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 AIIRA 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 also sections 4.3 and 4.4)

**Lactation:** Because no information is available regarding the use of irbesartan during breastfeeding, irbesartan is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a new born or preterm infant.

**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.

**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.
Cardiac disorders:
Uncommon: tachycardia

Nervous system disorders:
Common: dizziness, orthostatic dizziness*

Respiratory, thoracic and mediastinal disorders:
Uncommon: cough

Gastrointestinal disorders:
Common: nausea/vomiting
Uncommon: diarrhoea, dyspepsia/heartburn

Musculoskeletal and connective tissue disorders:
Common: musculoskeletal pain*

Vascular disorders:
Common: orthostatic hypotension*
Uncommon: flushing

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

Reproductive system and breast disorders:
Uncommon: sexual dysfunction

The following additional adverse reactions have been reported during post-marketing experience; they are derived from spontaneous reports and therefore, the frequency of these adverse reactions is not known:

Nervous system disorders:
Headache

Ear and labyrinth disorders:
Tinnitus

Gastrointestinal disorders:
Dysgeusia

Renal and urinary disorders:
Impaired renal function including cases of renal failure in patients at risk (see section 4.4)

Skin and subcutaneous tissue disorders:
Leukocytoclastic vasculitis

Musculoskeletal and connective tissue disorders:
Arthralgia, myalgia (in some cases associated with increased plasma creatine kinase levels), muscle cramps

Metabolism and nutrition disorders:
Hyperkalemia

Immune system disorders:
Hypersensitivity reactions such as angioedema, rash, urticaria

Hepato-biliary disorders:
Hepatitis, abnormal liver function
**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 overdosage are expected to be hypotension and tachycardia; bradycardia might also occur from overdose. No specific information is available on the treatment of overdosage 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 overdosage. Irbesartan is not removed by haemodialysis.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**
Pharmacotherapeutic group: Angiotensin-II antagonists, plain.

ATC code C09C A04.

**Mechanism of action:** 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.

**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.
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 $^{14}$C 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 $^{14}$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.

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.

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:
- Croscarmellose sodium
- Microcrystalline Cellulose
- Hypermellose
- Mannitol
- Magnesium stearate, non-bovine
- Silica, colloidal anhydrous

Tablet coating:
- Hydroxypropyl cellulose
- Hypermellose
- Polyethylene glycol
- Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Blister packs (Al/PVDC blisters)
Tablet containers (HDPE) with desiccant and LDPE cap

Pack sizes:

Blisters:
- Irbesartan 150 mg film-coated tablets: 14, 28, 30, 56, 84, 90, 98 tablets

Tablet containers:
- Irbesartan 150 mg film-coated tablets: 14, 28, 30, 56, 84, 90, 98 tablets

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
Caduceus Pharma Limited
6th floor
94 Wigmore Street
London
W1U 3 RF

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0107

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
04/04/2011

10 DATE OF REVISION OF THE TEXT
04/04/2011
NAME OF THE MEDICINAL PRODUCT
Irbesartan 300 mg film-coated tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 300 mg irbesartan.

For a full list of excipients, see section 6.1.

PHARMACEUTICAL FORM
Film-coated tablet.

The 300 mg tablets are white, elliptical, biconvex, film-coated, with diameter of 8.2 x 16.0 mm, marked 'I' on one side and '300' on the other side.

CLINICAL PARTICULARS

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

Posology and method of administration
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).

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: irbesartan is not recommended for use in children and adolescents due to insufficient data on safety and efficacy (see sections 5.1 and 5.2).

Contraindications
Hypersensitivity to the active substance 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 drugs 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).

**Hyperkalemia:** as with other drugs that affect the renin-angiotensin-aldosterone system, hyperkalemia 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 anti-hypertensive 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 4.4 and 4.6).
**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

**Inadvisable combinations**

**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 pharmacokinetic 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 drug 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 trimesters 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 AIIRA 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 also sections 4.3 and 4.4)

**Lactation:** Because no information is available regarding the use of irbesartan during breastfeeding, irbesartan is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a new born or preterm infant.

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.

**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.
Cardiac disorders:
Uncommon: tachycardia

Nervous system disorders:
Common: dizziness, orthostatic dizziness*

Respiratory, thoracic and mediastinal disorders:
Uncommon: cough

Gastrointestinal disorders:
Common: nausea/vomiting
Uncommon: diarrhoea, dyspepsia/heartburn

Musculoskeletal and connective tissue disorders:
Common: musculoskeletal pain*

Vascular disorders:
Common: orthostatic hypotension*
Uncommon: flushing

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

Reproductive system and breast disorders:
Uncommon: sexual dysfunction

The following additional adverse reactions have been reported during post-marketing experience; they are derived from spontaneous reports and therefore, the frequency of these adverse reactions is not known:

Nervous system disorders:
Headache

Ear and labyrinth disorders:
Tinnitus

Gastrointestinal disorders:
Dysgeusia

Renal and urinary disorders:
Impaired renal function including cases of renal failure in patients at risk (see section 4.4)

Skin and subcutaneous tissue disorders:
Leukocytoclastic vasculitis

Musculoskeletal and connective tissue disorders:
Arthralgia, myalgia (in some cases associated with increased plasma creatine kinase levels), muscle cramps

Metabolism and nutrition disorders:
Hyperkalemia

Immune system disorders:
Hypersensitivity reactions such as angioedema, rash, urticaria

Hepato-biliary disorders:
Hepatitis, abnormal liver function


**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 overdosage are expected to be hypotension and tachycardia; bradycardia might also occur from overdose. No specific information is available on the treatment of overdosage 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 C09C A04.

**Mechanism of action:** 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.

**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.
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.

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.

Animal studies with irbesartan showed transient toxic effects (increased renal pelvic cavitation, hydrourerter 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:
- Croscarmellose sodium
- Microcrystalline Cellulose
- Hypromellose
- Mannitol
- Magnesium stearate, non-bovine
- Silica, colloidal anhydrous

Tablet coating:
- Hydroxypropyl cellulose
- Hypromellose
- Polyethylene glycol
- Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Blister packs (Al/PVDC blisters)
Tablet containers (HDPE) with desiccant and LDPE cap

Pack sizes:

Blisters:
Irbesartan 300 mg film-coated tablets: 14, 28, 30, 56, 84, 90, 98 tablets

Tablet containers:
Irbesartan 300 mg film-coated tablets: 14, 28, 30, 56, 84, 90, 98 tablets

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
Caduceus Pharma Limited
6th floor
94 Wigmore Street
London
W1U 3 RF

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0108

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
04/04/2011

10 DATE OF REVISION OF THE TEXT
04/04/2011
PATIENT INFORMATION LEAFLET

Irbesartan 75mg, 150mg & 300mg film-coated tablets

Irbesartan

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 gets serious, 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 IRBESARTAN 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:
• in the treatment of high blood pressure (hypertension)
• to protect the kidney in patients with high blood pressure, type 2 diabetes and known 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.)

Take special care with Irbesartan
• if you suffer from excessive vomiting or diarrhoea
• if you suffer from kidney problems
• if you suffer from heart problems
• if you receive irbesartan for diabetic renal 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 to undergo any surgery or receive anaesthetics, you should also tell your doctor about it

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 if used 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.

Irbetasratan does not usually interact with other medicines. Special precautionary measures (e.g. blood tests) may be appropriate if you take potassium supplements, potassium-containing salt substitutes, potassium-sparing medicines (such as certain diuretics) or lithium-containing medicines.
The effect of irbesartan may be reduced when you take non-steroidal anti-inflammatory drugs (certain pain killers).

Taking irbesartan with food and drink
Irbetasratan can be taken with or without food. The tablets should be swallowed with a drink of water.

Pregnancy and breastfeeding
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. Irbetasratan 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
Irbetasratan 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, you should consult your doctor before attempting such activities.

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.

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

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. Irbetasratan is for oral use and is taken with or without food. The tablets should be swallowed with a drink of water. You should 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.

Irbetasratan should not be given to children (< 18 years).
**If you take more irbesartan than you should**
If you accidentally take too many tablets, or a child swallows some, 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 called creatine kinase that can indicate muscle damage. 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: 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 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 gets serious, 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.

This medicinal product does not require any 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

If you would like more information on your disease or treatment, you should ask your doctor or pharmacist.

What irbesartan contains

- The active substance is irbesartan. Each tablet contains 75 mg, 150 mg or 300 mg of irbesartan.
- The other ingredients are: croscarmellose sodium, microcrystalline cellulose, hypromellose, mannitol, magnesium stearate, silica, colloidal anhydrous, hydroxypropyl cellulose, polyethylene glycol, titanium dioxide

What irbesartan looks like and contents of the pack

The 75 mg tablets are white, elliptical, biconvex, film-coated, with diameter of 5.2 x 10 mm, marked ‘I’ on one side and ‘75’ on the other side.

The 150 mg tablets are white, elliptical, biconvex, film-coated, with diameter of 6.5 x 12.7 mm, marked ‘I’ on one side and ‘150’ on the other side.

The 300 mg tablets are white, elliptical, biconvex, film-coated, with diameter of 8.2 x 16.0 mm, marked ‘I’ on one side and ‘300’ on the other side.

Pack sizes:

Blister: 14, 28, 30, 56, 84, 90, 98 film-coated tablets
Tablet containers: 14, 28, 30, 56, 84, 90, 98 film-coated tablets

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Caduceus Pharma Limited
6th floor
94 Wigmore Street
London
W1U 3RF

Manufacturer:
Actavis hf.
Reykjavikurvegi 78
PO Box 420
IS-220 Hafnarfjordur
Iceland

This leaflet was last updated in 10/2010
## LABELLING

### PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Carton for blister

### 1. NAME OF THE MEDICINAL PRODUCT

Irbesartan 75 mg film-coated tablets

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains: irbesartan 75 mg.

### 3. LIST OF EXCIPIENTS

### 4. PHARMACEUTICAL FORM AND CONTENTS

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>film-coated tablets</td>
</tr>
<tr>
<td>28</td>
<td>film-coated tablets</td>
</tr>
<tr>
<td>30</td>
<td>film-coated tablets</td>
</tr>
<tr>
<td>56</td>
<td>film-coated tablets</td>
</tr>
<tr>
<td>84</td>
<td>film-coated tablets</td>
</tr>
<tr>
<td>90</td>
<td>film-coated tablets</td>
</tr>
<tr>
<td>98</td>
<td>film-coated tablets</td>
</tr>
</tbody>
</table>

### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

### 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

### 8. EXPIRY DATE

EXP

### 9. SPECIAL STORAGE CONDITIONS
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited
6th floor
94 Wigmore Street
London
W1U 3RF

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0106

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

irbesartan 75 mg film-coated tablets
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Tablet Container

1. NAME OF THE MEDICINAL PRODUCT

Irbesartan 75 mg film-coated tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains: irbesartan 75 mg.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
56 film-coated tablets
84 film-coated tablets
90 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
<table>
<thead>
<tr>
<th>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caduceus Pharma Limited</td>
</tr>
<tr>
<td>6th floor</td>
</tr>
<tr>
<td>94 Wigmore Street</td>
</tr>
<tr>
<td>London</td>
</tr>
<tr>
<td>W1U 3RF</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>12. MARKETING AUTHORISATION NUMBER(S)</td>
</tr>
<tr>
<td>PL 24668/0106</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>13. BATCH NUMBER</td>
</tr>
<tr>
<td>Lot</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>14. GENERAL CLASSIFICATION FOR SUPPLY</td>
</tr>
<tr>
<td>POM</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>15. INSTRUCTIONS ON USE</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>16. INFORMATION IN BRAILLE</td>
</tr>
<tr>
<td>irbesartan 75 mg film-coated tablets</td>
</tr>
<tr>
<td><strong>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</strong></td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></td>
</tr>
<tr>
<td>Irbesartan 75 mg film-coated tablets</td>
</tr>
<tr>
<td><strong>2. NAME OF THE MARKETING AUTHORISATION HOLDER</strong></td>
</tr>
<tr>
<td>Caduceus Pharma Limited</td>
</tr>
<tr>
<td><strong>3. EXPIRY DATE</strong></td>
</tr>
<tr>
<td>EXP</td>
</tr>
<tr>
<td><strong>4. BATCH NUMBER</strong></td>
</tr>
<tr>
<td>Lot</td>
</tr>
<tr>
<td><strong>5. OTHER</strong></td>
</tr>
</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Carton for blister

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irbesartan 150 mg film-coated tablets</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each film-coated tablet contains: irbesartan 150 mg.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 film-coated tablets</td>
</tr>
<tr>
<td>28 film-coated tablets</td>
</tr>
<tr>
<td>30 film-coated tablets</td>
</tr>
<tr>
<td>56 film-coated tablets</td>
</tr>
<tr>
<td>84 film-coated tablets</td>
</tr>
<tr>
<td>90 film-coated tablets</td>
</tr>
<tr>
<td>98 film-coated tablets</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral use. Read the package leaflet before use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the reach and sight of children.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>8. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
</tr>
</thead>
</table>
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

   Caduceus Pharma Limited  
   6th floor  
   94 Wigmore Street  
   London  
   W1U 3RF

12. **MARKETING AUTHORISATION NUMBER(S)**

   PL 24668/0107

13. **BATCH NUMBER**

   Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

   POM

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

   irbesartan 150 mg film-coated tablets
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**Tablet Container**

<table>
<thead>
<tr>
<th><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Irbesartan 150 mg film-coated tablets</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>2. STATEMENT OF ACTIVE SUBSTANCE(S)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Each film-coated tablet contains: irbesartan 150 mg.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>3. LIST OF EXCIPIENTS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>4. PHARMACEUTICAL FORM AND CONTENTS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>14 film-coated tablets</td>
</tr>
<tr>
<td>28 film-coated tablets</td>
</tr>
<tr>
<td>30 film-coated tablets</td>
</tr>
<tr>
<td>56 film-coated tablets</td>
</tr>
<tr>
<td>84 film-coated tablets</td>
</tr>
<tr>
<td>90 film-coated tablets</td>
</tr>
<tr>
<td>98 film-coated tablets</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>5. METHOD AND ROUTE(S) OF ADMINISTRATION</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral use. Read the package leaflet before use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the reach and sight of children.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>7. OTHER SPECIAL WARNING(S), IF NECESSARY</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>8. EXPIRY DATE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>9. SPECIAL STORAGE CONDITIONS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</strong></th>
</tr>
</thead>
</table>
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited  
6th floor  
94 Wigmore Street  
London  
W1U 3RF

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0107

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

irbesartan 150 mg film-coated tablets
UKPAR Irbesartan 75, 150 and 300mg Film-coated Tablets

<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></td>
</tr>
<tr>
<td>Irbesartan 150 mg film-coated tablets</td>
</tr>
<tr>
<td><strong>2. NAME OF THE MARKETING AUTHORISATION HOLDER</strong></td>
</tr>
<tr>
<td>Caduceus Pharma Limited</td>
</tr>
<tr>
<td><strong>3. EXPIRY DATE</strong></td>
</tr>
<tr>
<td>EXP</td>
</tr>
<tr>
<td><strong>4. BATCH NUMBER</strong></td>
</tr>
<tr>
<td>Lot</td>
</tr>
<tr>
<td><strong>5. OTHER</strong></td>
</tr>
</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Carton for blister

1. NAME OF THE MEDICINAL PRODUCT

Irbesartan 300 mg film-coated tablets
Irbesartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains: irbesartan 300 mg.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
56 film-coated tablets
84 film-coated tablets
90 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited
8th floor
94 Wigmore Street
London
W1U 3RF

12. MARKETING AUTHORISATION NUMBER(S)

PL24668/0108

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Irbesartan 300 mg film-coated tablets
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Tablet Container

1. NAME OF THE MEDICINAL PRODUCT

Irbesartan 300 mg film-coated tablets
Irbesartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains: irbesartan 300 mg.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
56 film-coated tablets
84 film-coated tablets
90 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Cedacess Pharma Limited
6th floor
94 Wigmore Street
London
W1U 3RF

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0108

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Irbesartan 300 mg film-coated tablets
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. NAME OF THE MEDICINAL PRODUCT</td>
</tr>
<tr>
<td>Irbesartan 300 mg film-coated tablets</td>
</tr>
<tr>
<td>Irbesartan</td>
</tr>
<tr>
<td>2. NAME OF THE MARKETING AUTHORISATION HOLDER</td>
</tr>
<tr>
<td>Caduceus Pharma Limited</td>
</tr>
<tr>
<td>3. EXPIRY DATE</td>
</tr>
<tr>
<td>EXP</td>
</tr>
<tr>
<td>4. BATCH NUMBER</td>
</tr>
<tr>
<td>Lot</td>
</tr>
<tr>
<td>5. OTHER</td>
</tr>
</tbody>
</table>