Public Assessment Report

Decentralised Procedure

IRBESARTAN 75MG FILM-COATED TABLETS
IRBESARTAN 150MG FILM-COATED TABLETS
IRBESARTAN 300MG FILM-COATED TABLETS

(Irbesartan)

Procedure No: UK/H/3094/001-3/DC

UK Licence No: PL 33786/0002-4

ARROW APS.
LAY SUMMARY

On 21 March 2012, the Czech Republic, Germany, Denmark, Greece, Spain, Finland, France, Ireland, Italy, Malta, Netherlands, Norway, Sweden and the UK agreed to grant Marketing Authorisations to Arrow ApS for the medicinal products Irbesartan 75mg, 150mg and 300mg Film-coated Tablets (PL 33786/0002-4; UK/H/3094/001-3/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, Marketing Authorisations were granted in the UK on 24 April 2012. These are Prescription-Only Medicines (POM).

Irbesartan belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin II is a substance produced in the body which binds to receptors in blood vessels causing them to tighten. This results in an increase in blood pressure. Irbesartan prevents the binding of angiotensin II to these receptors, causing the blood vessels to relax and the blood pressure to lower.

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

This medicine is used in adult patients to:

- treat high blood pressure (essential hypertension).
- protect the kidney in patients with high blood pressure, type 2 diabetes and laboratory evidence of impaired kidney function.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Irbesartan 75mg, 150mg and 300mg Film-coated Tablets outweigh the risks and Marketing Authorisations were granted.
TABLE OF CONTENTS

Module 1: Information about initial procedure  Page 4
Module 2: Summary of Product Characteristics  Page 5
Module 3: Product Information Leaflet  Page 45
Module 4: Labelling  Page 47
Module 5: Scientific discussion during initial procedure  Page 52
   I Introduction
   II About the product
   III Scientific Overview and discussion
      III.1 Quality aspects
      III.2 Non-clinical aspects
      III.3 Clinical aspects
   IV Overall Conclusions and benefit-risk assessment
Module 6  Steps taken after initial procedure  Page 61
## Module 1

| **Product Name** | Irbesartan 75mg Film-coated Tablets  
Irbesartan 150mg Film-coated Tablets  
Irbesartan 300mg Film-coated Tablets |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substances</strong></td>
<td>Irbesartan</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Film-coated tablets</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>75 mg, 150 mg and 300 mg.</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Arrow ApS, Sankt Peders Stræde 2,1., 4000 Roskilde, Denmark.</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>Concerned Member State (CMS)</strong></td>
<td>Czech Republic, Germany, Denmark, Greece, Spain, Finland, France, Ireland, Italy, Malta, Netherlands, Norway, Sweden</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/3094/001-3/DC</td>
</tr>
<tr>
<td><strong>Timetable</strong></td>
<td>Day 210–21 March 2012.</td>
</tr>
</tbody>
</table>
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Irbesartan 75mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 75 mg of irbesartan.
Excipient: 15.5 mg of lactose monohydrate per film-coated tablet.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Description:
Irbesartan 75 mg film-coated tablets are white, approximately 5.0 x 9.8 mm oval shaped coated tablet with ‘IS’ on one side and ‘©’ 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

Posology:
The usual recommended initial and maintenance dose is 150 mg once daily, with or without food. Irbesartan at a dose of 150 mg once daily generally provides a better 24 hour blood pressure control than 75 mg. However, initiation of therapy with 75 mg could be considered, particularly in haemodialysed patients and in the elderly over 75 years.
In patients insufficiently controlled with 150 mg once daily, the dose of Irbesartan can be increased to 300 mg, or other antihypertensive agents can be added. In particular, the addition of a diuretic such as hydrochlorothiazide has been shown to have an additive effect with Irbesartan (see section 4.5).
In hypertensive type 2 diabetic patients, therapy should be initiated at 150 mg irbesartan once daily and titrated up to 300 mg once daily as the preferred maintenance dose for treatment of renal disease. The demonstration of renal benefit of Irbesartan in hypertensive type 2 diabetic patients is based on studies where irbesartan was used in addition to other antihypertensive agents, as needed, to reach target blood pressure (see section 5.1).

Special Populations:

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

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

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

Paediatric Population: The safety and efficacy of Irbesartan Film-coated Tablets in children aged 0 to 18 has not been established. Currently available data are described in sections 4.8, 5.1, and 5.2 but no recommendation on a posology can be made.
Method of administration:
For oral use

4.3 Contraindications
Hypersensitivity to the active substance, or to any of the excipients (see section 6.1). Second and third trimesters of pregnancy (see sections 4.4 and 4.6).

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

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

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

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

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

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

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy: as with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Primary aldosteronism: patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of Irbesartan is not recommended.

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

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

Pregnancy: Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Lactose: this medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
Paediatric Population: Irbesartan has been studied in paediatric populations aged 6 to 16 years old but the current data are insufficient to support an extension of the use in children until further data become available (see sections 4.8, 5.1 and 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

Non-steroidal anti-inflammatory drugs: when angiotensin II antagonists are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.

As with ACE inhibitors, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Additional information on irbesartan interactions: in clinical studies, the 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 medicinal product metabolised by CYP2C9. The effects of CYP2C9 inducers such as rifampicin on the pharmacokinetic of irbesartan have not been evaluated. The pharmacokinetic of digoxin was not altered by co administration of Irbesartan.

4.6 Fertility, 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 AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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 sections 4.3 and 4.4).

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

It is unknown whether irbesartan or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in rats have shown excretion of irbesartan or its metabolites in milk (for details see 5.3).

Fertility: Irbesartan had no effect upon fertility of treated rats and their offspring up to the dose levels inducing the first signs of parental toxicity (see section 5.3).

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

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

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

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

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders:</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity reactions such as angioedema, rash, urticaria</td>
<td>Very common (≥ 1/10); common (≥ 1/100, &lt; 1/10); uncommon (≥ 1/1,000, &lt; 1/100); rare (≥ 1/10,000, &lt; 1/1,000); very rare (&lt; 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders:</td>
<td></td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>Very common (≥ 1/10); common (≥ 1/100, &lt; 1/10); uncommon (≥ 1/1,000, &lt; 1/100); rare (≥ 1/10,000, &lt; 1/1,000); very rare (&lt; 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.</td>
</tr>
<tr>
<td>Nervous system disorders:</td>
<td></td>
</tr>
<tr>
<td>Dizziness, orthostatic dizziness*</td>
<td>Very common (≥ 1/10); common (≥ 1/100, &lt; 1/10); uncommon (≥ 1/1,000, &lt; 1/100); rare (≥ 1/10,000, &lt; 1/1,000); very rare (&lt; 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.</td>
</tr>
<tr>
<td>Ear and labyrinth disorder:</td>
<td></td>
</tr>
<tr>
<td>Tinnitus</td>
<td>Very common (≥ 1/10); common (≥ 1/100, &lt; 1/10); uncommon (≥ 1/1,000, &lt; 1/100); rare (≥ 1/10,000, &lt; 1/1,000); very rare (&lt; 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.</td>
</tr>
<tr>
<td>Cardiac disorders:</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Very common (≥ 1/10); common (≥ 1/100, &lt; 1/10); uncommon (≥ 1/1,000, &lt; 1/100); rare (≥ 1/10,000, &lt; 1/1,000); very rare (&lt; 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.</td>
</tr>
<tr>
<td>Vascular disorders:</td>
<td></td>
</tr>
</tbody>
</table>

Adverse reactions additionally reported from post-marketing experience are also listed. These adverse reactions are derived from spontaneous reports.
Common: orthostatic hypotension*
Uncommon: flushing

**Respiratory, thoracic and mediastinal disorders:**
Uncommon: cough

**Gastrointestinal disorders:**
Common: nausea/vomiting
Uncommon: diarrhoea, dyspepsia/heartburn
Not known: dysgeusia

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

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

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

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

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

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

**Investigations:**
Very common: Hyperkalaemia* occurred more often in diabetic patients treated with irbesartan than with placebo. In diabetic hypertensive patients with microalbuminuria and normal renal function, hyperkalaemia (≥ 5.5 mEq/L) occurred in 29.4% of the patients in the irbesartan 300 mg group and 22% of the patients in the placebo group. In diabetic hypertensive patients with chronic renal insufficiency and overt proteinuria, hyperkalaemia (≥ 5.5 mEq/L) occurred in 46.3% of the patients in the irbesartan group and 26.3% of the patients in the placebo group.
Common: significant increases in plasma creatine kinase were commonly observed (1.7%) in irbesartan treated subjects. None of these increases were associated with identifiable clinical musculoskeletal events. In 1.7% of hypertensive patients with advanced diabetic renal disease treated with irbesartan, a decrease in haemoglobin*, which was not clinically significant, has been observed.

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

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

**5 PHARMACOLOGICAL PROPERTIES**
5.1 Pharmacodynamic properties

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

Paediatric population:

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

Hypertension and type 2 diabetes with renal disease

The “Irbesartan Diabetic Nephropathy Trial (IDNT)” shows that irbesartan decreases the progression of renal disease in patients with chronic renal insufficiency and overt proteinuria. IDNT was a double
blinded, 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 allcause mortality. Approximately 33% of patients in the irbesartan group reached the primary renal composite endpoint compared to 39% and 41% in the placebo and amlodipine groups [20% relative risk reduction versus placebo (p = 0.024) and 23% relative risk reduction compared to amlodipine (p = 0.006)]. When the individual components of the primary endpoint were analysed, no effect in all cause mortality was observed, while a positive trend in the reduction in ESRD and a significant reduction in doubling of serum creatinine were observed.

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

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

5.2 Pharmacokinetic properties

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

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

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

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

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

Hepatic impairment: in patients with mild to moderate cirrhosis, the pharmacokinetic parameters of irbesartan are not significantly altered. Studies have not been performed in patients with severe hepatic impairment.

5.3 Preclinical safety data
There was no evidence of abnormal systemic or target organ toxicity at clinically relevant doses. In non-clinical safety studies, high doses of irbesartan (≥ 250 mg/kg/day in rats and ≥ 100 mg/kg/day in macaques) caused a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit).

At very high doses (≥ 500 mg/kg/day) degenerative changes in the kidney (such as interstitial nephritis, tubular distension, basophilic tubules, increased plasma concentrations of urea and creatinine) were induced by irbesartan in the rat and the macaque and are considered secondary to the hypotensive effects of the medicinal product which led to decreased renal perfusion. Furthermore, irbesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells (in rats at ≥ 90 mg/kg/day, in macaques at ≥ 10 mg/kg/day). All of these changes were considered to be caused by the pharmacological action of irbesartan. For therapeutic doses of irbesartan in humans, the hyperplasia/hypertrophy of the renal juxtaglomerular cells does not appear to have any relevance.

There was no evidence of mutagenicity, clastogenicity or carcinogenicity.

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

Studies in animals indicate that the radiolabeled irbesartan is detected in rat and rabbit fetuses. Irbesartan is excreted in the milk of lactating rats.

Animal studies with irbesartan showed transient toxic effects (increased renal pelvic caviation, 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:
Cellulose, microcrystalline  
Lactose monohydrate  
Crospovidone (Type A)  
Hydroxypropylcellulose  
Talc (E553b)  
Sodium stearyl fumarate.

**Film-coating:**  
Polyvinyl alcohol, partially hydrolysed  
Titanium dioxide (E171)  
Macrogol 3350  
Talc (E553b)

6.2 **Incompatibilities**  
Not applicable.

6.3 **Shelf life**  
15 months

6.4 **Special precautions for storage**  
Do not store above 25°C.  
Store in the original package in order to protect from light

6.5 **Nature and contents of container**  
The tablets are packed in PVC/PVDC/Aluminium foil blisters.  
Pack sizes:  
14, 28, 30, 56, 84, 90 or 98 film-coated tablets packed in an outer carton  
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**  
Arrow ApS, Sankt Peders Straede 2,1., 4000 Roskilde, Denmark

8 **MARKETING AUTHORISATION NUMBER(S)**  
PL 33786/0002

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**  
24/04/2012

10 **DATE OF REVISION OF THE TEXT**  
24/04/2012
1 NAME OF THE MEDICINAL PRODUCT
Irbesartan 150mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 150 mg of irbesartan.
Excipient: 31 mg of lactose monohydrate per film-coated tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Description:
Irbesartan 150 mg film-coated tablets are white, approximately 6.5 x 12.5mm, oval shaped coated tablet with ‘IS150’ on one side and ‘ ’ 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

Posology:
The usual recommended initial and maintenance dose is 150 mg once daily, with or without food. Irbesartan at a dose of 150 mg once daily generally provides a better 24 hour blood pressure control than 75 mg. However, initiation of therapy with 75 mg could be considered, particularly in haemodialysed patients and in the elderly over 75 years.

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

In hypertensive type 2 diabetic patients, therapy should be initiated at 150 mg irbesartan once daily and titrated up to 300 mg once daily as the preferred maintenance dose for treatment of renal disease. The demonstration of renal benefit of Irbesartan in hypertensive type 2 diabetic patients is based on studies where irbesartan was used in addition to other antihypertensive agents, as needed, to reach target blood pressure (see section 5.1).

Special Populations:

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

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

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

Paediatric Population: The safety and efficacy of Irbesartan Film-coated Tablets in children aged 0 to 18 has not been established. Currently available data are described in sections 4.8, 5.1, and 5.2 but no recommendation on a posology can be made.

Method of administration:
For oral use
4.3 Contraindications
Hypersensitivity to the active substance, or to any of the excipients (see section 6.1).
Second and third trimesters of pregnancy (see sections 4.4 and 4.6).

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

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

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

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

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

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

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy: as with other vasodilators,
special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive
hypertrophic cardiomyopathy.

Primary aldosteronism: patients with primary aldosteronism generally will not respond to
antihypertensive medicinal products acting through inhibition of the renin-angiotensin system.
Therefore, the use of Irbesartan is not recommended.

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

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

Pregnancy: Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy.
Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be
changed to alternative antihypertensive treatments which have an established safety profile for use in
pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and,
if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

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

Paediatric Population: Irbesartan has been studied in paediatric populations aged 6 to 16 years old but
the current data are insufficient to support an extension of the use in children until further data become
available (see sections 4.8, 5.1 and 5.2).
4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

Non-steroidal anti-inflammatory drugs: when angiotensin II antagonists are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.

As with ACE inhibitors, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Additional information on irbesartan interactions: in clinical studies, the 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 medicinal product metabolised by CYP2C9. The effects of CYP2C9 inducers such as rifampicin on the pharmacokinetic of irbesartan have not been evaluated. The pharmacokinetic of digoxin was not altered by co administration of Irbesartan.

4.6 Fertility, 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 AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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 sections 4.3 and 4.4).
Lactation:

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

It is unknown whether irbesartan or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in rats have shown excretion of irbesartan or its metabolites in milk (for details see 5.3).

Fertility:

Irbesartan had no effect upon fertility of treated rats and their offspring up to the dose levels inducing the first signs of parental toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

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

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

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

**Immune system disorders:**
Not known: hypersensitivity reactions such as angioedema, rash, urticaria

**Metabolism and nutrition disorders:**
Not known: hyperkalaemia

**Nervous system disorders:**
Common: dizziness, orthostatic dizziness*
Not known: vertigo, headache

**Ear and labyrinth disorder:**
Not known: tinnitus

**Cardiac disorders:**
Uncommon: tachycardia

**Vascular disorders:**
Common: orthostatic hypotension*
Uncommon: flushing
Respiratory, thoracic and mediastinal disorders:
Uncommon: cough

Gastrointestinal disorders:
Common: nausea/vomiting
Uncommon: diarrhoea, dyspepsia/heartburn
Not known: dysgeusia

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

Skin and subcutaneous tissue disorders:
Not known: leukocytoclastic vasculitis

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

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

Reproductive system and breast disorders:
Uncommon: sexual dysfunction

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

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

Common: significant increases in plasma creatine kinase were commonly observed (1.7%) in irbesartan treated subjects. None of these increases were associated with identifiable clinical musculoskeletal events. In 1.7% of hypertensive patients with advanced diabetic renal disease treated with irbesartan, a decrease in haemoglobin*, which was not clinically significant, has been observed.

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

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

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Angiotensin-II antagonists, plain.
ATC code: 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.

Paediatric population:

Reduction of blood pressure with 0.5 mg/kg (low), 1.5 mg/kg (medium) and 4.5 mg/kg (high) target titrated doses of irbesartan was evaluated in 318 hypertensive 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 amloidipine, 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 amloidipine groups respectively. Irbesartan significantly reduced the relative risk in the primary combined endpoint of doubling serum creatinine, end-stage renal disease (ESRD) or allcause mortality. Approximately 33% of patients in the irbesartan group reached the primary renal composite endpoint compared to 39% and 41% in the placebo and amloidipine groups [20% relative risk reduction versus placebo (p = 0.024) and 23% relative risk reduction compared to amloidipine (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 amloidipine-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/dl) and normal renal function (serum creatinine ≤ 1.5 mg/dl in males and < 1.1 mg/dl in females). The study examined the long-term effects (2 years) of Irbesartan on the progression to clinical (overt) proteinuria (urinary albumin excretion rate (UAER) > 300 mg/day, and an increase in UAER of at least 30% from baseline). The predefined blood pressure goal was ≤ 135/85 mmHg. Additional antihypertensive agents (excluding ACE inhibitors, angiotensin II receptor antagonists and dihydropyridine calcium blockers) were added as needed to help achieve the blood pressure goal. While similar blood pressure was achieved in all treatment groups, fewer subjects in the irbesartan 300 mg group (5.2%) than in the placebo (14.9%) or in the irbesartan 150 mg group (9.7%) reached the endpoint of overt proteinuria, demonstrating a 70% relative risk reduction versus placebo (p = 0.0004) for the higher dose. An accompanying improvement in the glomerular filtration rate (GFR) was not observed during the first three months of treatment. The slowing in the progression to clinical proteinuria was evident as early as three months and continued over the 2 year period. Regression to normoalbuminuria (< 30 mg/day) was more frequent in the Irbesartan 300 mg group (34%) than in the placebo group (21%).

### 5.2 Pharmacokinetic properties

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

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

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

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

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

Hepatic impairment: in patients with mild to moderate cirrhosis, the pharmacokinetic parameters of irbesartan are not significantly altered. Studies have not been performed in patients with severe hepatic impairment.

5.3 Preclinical safety data

There was no evidence of abnormal systemic or target organ toxicity at clinically relevant doses. In non-clinical safety studies, high doses of irbesartan (≥ 250 mg/kg/day in rats and ≥ 100 mg/kg/day in macaques) caused a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit).

At very high doses (≥ 500 mg/kg/day) degenerative changes in the kidney (such as interstitial nephritis, tubular distension, basophilic tubules, increased plasma concentrations of urea and creatinine) were induced by irbesartan in the rat and the macaque and are considered secondary to the hypotensive effects of the medicinal product which led to decreased renal perfusion. Furthermore, irbesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells (in rats at ≥ 90 mg/kg/day, in macaques at ≥ 10 mg/kg/day). All of these changes were considered to be caused by the pharmacological action of irbesartan. For therapeutic doses of irbesartan in humans, the hyperplasia/hypertrophy of the renal juxtaglomerular cells does not appear to have any relevance.

There was no evidence of mutagenicity, clastogenicity or carcinogenicity.

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

Studies in animals indicate that the radiolabeled irbesartan is detected in rat and rabbit fetuses. Irbesartan is excreted in the milk of lactating rats.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose, microcrystalline
Lactose monohydrate
Crospovidone (Type A)
Hydroxypropylcellulose
Talc (E553b)
Sodium stearyl fumarate.

Film-coating:
Polyvinyl alcohol, partially hydrolysed
Titanium dioxide (E171)
Macrogol 3350
Talc (E553b)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
15 months

6.4 Special precautions for storage
Do not store above 25°C.
Store in the original package in order to protect from light

6.5 Nature and contents of container
The tablets are packed in PVC/PVDC/Aluminium foil blisters.

Pack sizes:
14, 28, 30, 56, 84, 90 or 98 film-coated tablets packed in an outer carton

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
Arrow ApS, Sankt Peders Straede 2,1., 4000 Roskilde, Denmark

8 MARKETING AUTHORISATION NUMBER(S)
PL 33786/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24/04/2012

10 DATE OF REVISION OF THE TEXT
24/04/2012
1 NAME OF THE MEDICINAL PRODUCT
Irbesartan 300mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 300 mg of irbesartan.
Excipient: 62 mg of lactose monohydrate per film-coated tablet.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Description:
Irbesartan 300 mg film-coated tablets are white, approximately 8.0 x 15.5mm oval shaped coated tablet with ‘IS300’ on one side and ‘’ 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
Posology:
The usual recommended initial and maintenance dose is 150 mg once daily, with or without food. Irbesartan at a dose of 150 mg once daily generally provides a better 24 hour blood pressure control than 75 mg. However, initiation of therapy with 75 mg could be considered, particularly in haemodialysed patients and in the elderly over 75 years.

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

In hypertensive type 2 diabetic patients, therapy should be initiated at 150 mg irbesartan once daily and titrated up to 300 mg once daily as the preferred maintenance dose for treatment of renal disease. The demonstration of renal benefit of Irbesartan in hypertensive type 2 diabetic patients is based on studies where irbesartan was used in addition to other antihypertensive agents, as needed, to reach target blood pressure (see section 5.1).

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

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

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

Paediatric Population: The safety and efficacy of Irbesartan Film-coated Tablets in children aged 0 to 18 has not been established. Currently available data are described in sections 4.8, 5.1, and 5.2 but no recommendation on a posology can be made.

Method of administration:
For oral use
4.3 Contraindications

Hypersensitivity to the active substance, or to any of the excipients (see section 6.1).
Second and third trimesters of pregnancy (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

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

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

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

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

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

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

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy: as with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Primary aldosteronism: patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of Irbesartan is not recommended.

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

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

Pregnancy: Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Lactose: this medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
Paediatric Population: Irbesartan has been studied in paediatric populations aged 6 to 16 years old but the current data are insufficient to support an extension of the use in children until further data become available (see sections 4.8, 5.1 and 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

Non-steroidal anti-inflammatory drugs: when angiotensin II antagonists are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.

As with ACE inhibitors, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Additional information on irbesartan interactions: in clinical studies, the 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 medicinal product metabolised by CYP2C9. The effects of CYP2C9 inducers such as rifampicin on the pharmacokinetic of irbesartan have not been evaluated. The pharmacokinetic of digoxin was not altered by co administration of Irbesartan.

4.6 Fertility, 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 AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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 sections 4.3 and 4.4).

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

It is unknown whether irbesartan or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in rats have shown excretion of irbesartan or its metabolites in milk (for details see 5.3).

**Fertility:**
Irbesartan had no effect upon fertility of treated rats and their offspring up to the dose levels inducing the first signs of parental toxicity (see section 5.3).

### 4.7 Effects on ability to drive and use machines

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

### 4.8 Undesirable effects

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

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

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

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

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

**Immune system disorders:**
Not known: hypersensitivity reactions such as angioedema, rash, urticaria

**Metabolism and nutrition disorders:**
Not known: hyperkalaemia

**Nervous system disorders:**
Common: dizziness, orthostatic dizziness*
Not known: vertigo, headache

**Ear and labyrinth disorder:**
Not known: tinnitus

**Cardiac disorders:**
Uncommon: tachycardia
Vascular disorders:
Common: orthostatic hypotension*
Uncommon: flushing

Respiratory, thoracic and mediastinal disorders:
Uncommon: cough

Gastrointestinal disorders:
Common: nausea/vomiting
Uncommon: diarrhoea, dyspepsia/heartburn
Not known: dysgeusia

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

Skin and subcutaneous tissue disorders:
Not known: leukocytoclastic vasculitis

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

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

Reproductive system and breast disorders:
Uncommon: sexual dysfunction

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

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

Common: significant increases in plasma creatine kinase were commonly observed (1.7%) in irbesartan treated subjects. None of these increases were associated with identifiable clinical musculoskeletal events. In 1.7% of hypertensive patients with advanced diabetic renal disease treated with irbesartan, a decrease in haemoglobin*, which was not clinically significant, has been observed.

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

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

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

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

Hypertension and type 2 diabetes with renal disease
The “Irbesartan Diabetic Nephropathy Trial (IDNT)” shows that irbesartan decreases the progression of renal disease in patients with chronic renal insufficiency and overt proteinuria. IDNT was a double
5.2 Pharmacokinetic properties

Irbesartan is primarily oxidised by the cytochrome P450 enzyme CYP2C9; isoenzyme CYP3A4 has negligible effect. 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

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
PAR Irbesartan 75mg, 150mg and 300mg Film-coated Tablets UK/H/3094/001-3/DC

3 - 3.5 ml/min, respectively. The terminal elimination half-life of irbesartan is 11 - 15 hours. Steady-state plasma concentrations are attained within 3 days after initiation of a once-daily dosing regimen. Limited accumulation of irbesartan (< 20%) is observed in plasma upon repeated once-daily dosing. In a study, somewhat higher plasma concentrations of irbesartan were observed in female hypertensive patients. However, there was no difference in the half-life and accumulation of irbesartan. No dosage adjustment is necessary in female patients. Irbesartan AUC and Cmax values were also somewhat greater in elderly subjects (≥ 65 years) than those of young subjects (18 - 40 years). However, the terminal half-life was not significantly altered. No dosage adjustment is necessary in elderly patients.

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

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

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

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

Studies have not been performed in patients with severe hepatic impairment

5.3 Preclinical safety data
There was no evidence of abnormal systemic or target organ toxicity at clinically relevant doses. In non-clinical safety studies, high doses of irbesartan (≥ 250 mg/kg/day in rats and ≥ 100 mg/kg/day in macaques) caused a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit).

At very high doses (≥ 500 mg/kg/day) degenerative changes in the kidney (such as interstitial nephritis, tubular distension, basophilic tubules, increased plasma concentrations of urea and creatinine) were induced by irbesartan in the rat and the macaque and are considered secondary to the hypotensive effects of the medicinal product which led to decreased renal perfusion. Furthermore, irbesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells (in rats at ≥ 90 mg/kg/day, in macaques at ≥ 10 mg/kg/day). All of these changes were considered to be caused by the pharmacological action of irbesartan. For therapeutic doses of irbesartan in humans, the hyperplasia/hypertrophy of the renal juxtaglomerular cells does not appear to have any relevance.

There was no evidence of mutagenicity, clastogenicity or carcinogenicity.

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

Studies in animals indicate that the radiolabeled irbesartan is detected in rat and rabbit fetuses. Irbesartan is excreted in the milk of lactating rats.

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

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients

Tablet core:
Cellulose, microcrystalline
Lactose monohydrate
Crospovidone (Type A)
Hydroxypropylcellulose
Talc (E553b)
Sodium stearyl fumarate.

Film-coating:
Polyvinyl alcohol, partially hydrolysed
Titanium dioxide (E171)
Macrogol 3350
Talc (E553b)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
15 months

6.4 Special precautions for storage
Do not store above 25°C.
Store in the original package in order to protect from light

6.5 Nature and contents of container
The tablets are packed in PVC/PVDC/Aluminium foil blisters.

Pack sizes:
14, 28, 30, 56, 84, 90 or 98 film-coated tablets packed in an outer carton

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
Arrow ApS, Sankt Peders Stræde 2,1., 4000 Roskilde, Denmark.

8 MARKETING AUTHORISATION NUMBER(S)
PL 33786/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24/04/2012

10 DATE OF REVISION OF THE TEXT
24/04/2012
Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER
Irbesartan 75 mg Film-coated Tablets
Irbesartan 150 mg Film-coated Tablets
Irbesartan 300 mg Film-coated Tablets

Irbesartan tablets are used to:
- treat high blood pressure (essential hypertension)
- protect the kidneys in patients with high blood pressure and type 2 diabetes
- protect the kidneys in patients with diabetic kidney disease.

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

1. BEFORE YOU TAKE IRBESARTAN TABLETS

Do not take Irbesartan Tablets:
- if you are allergic to irbesartan or any of the ingredients of Irbesartan Tablets.
- if you are more than 3 months pregnant (it is better to avoid Irbesartan Tablets in early pregnancy - see pregnancy section).

Use in children:
Irbesartan Tablets should not be given to children and adolescents under 18 years.

Take special care with Irbesartan Tablets:
- if you have liver problems.
- if you have heart failure.
- if you are taking any medicines that contain calcium channel blockers.

Use of medicines:
- tell your doctor or pharmacist if you are already taking any other medicines, including medicines obtained without a prescription.
- Irbesartan does not usually interact with other medicines.
- you may need to have blood checks if you take:
  - potassium supplements
  - salt substitutes containing potassium
  - potassium-blocking medicines (such as certain diuretics)
  - medicines containing lithium.

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

Pregnancy and breastfeeding:
- if you become pregnant while taking Irbesartan Tablets, contact your doctor immediately.
- if you are breastfeeding, contact your doctor before starting Irbesartan Tablets.

Driving and using machines:
- no studies have been done on this ability to drive and use machines.

Important information about some of the ingredients of Irbesartan Tablets:
Irbesartan Tablets contain lactose. If you have been told by your doctor that you have intolerance to some sugars (e.g., lactose), contact your doctor before taking this medicine.

3. HOW TO TAKE IRBESARTAN TABLETS

Always take Irbesartan Tablets exactly as your doctor has told you. If you are not sure, contact your doctor or pharmacist.

Method of administration:
Irbesartan Tablets are for oral use.
- swallow the tablets with a sufficient amount of fluid (e.g., glass of water).
- do not take Irbesartan Tablets with or without food. Try to take your daily dose at about the same time each day.

Side effects:

- some patients may experience dizziness or faintness after getting up quickly, especially if you have been lying down or sitting down. If this occurs, get up slowly, and make sure you are steady on your feet before getting up.
- some patients may experience a headache, which usually decreases with continued use of the medicine.
- some patients may experience a dry cough.
- some patients may experience a change in bowel habits or constipation.

If you experience any other side effects, contact your doctor or pharmacist. They may be able to help.

Children:
- children should not take Irbesartan Tablets.

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 an allergic skin reaction (e.g. angioedema), as well as localized 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 Tablets 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.
Uncertain: 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/nervous
- Fatigue
- Blood tests may show raised levels of an enzyme that measures the muscle and heart function (creatinine kinase enzyme).

In patients with high blood pressure and type 2 diabetes with kidney disease:
- Dizziness when getting up from a lying or sitting position
- Low blood pressure when getting up from a lying or sitting position
- Pains in joints or muscles
- Decreased level of a protein in the red blood cells (haemoglobin).

Uncertain:
- Heart rate increased
- Flashing
- Cough
- Diarrhoea
- Indigestion/heartburn
- Sexual dysfunction (problems with sexual performance)
- Chest pain.

Some undesirable effects have been reported since marketing of Irbesartan. Undesirable effects where the frequency is not known are:

- Feeling of opening
- Headache
- Taste disturbance
- Ringing in the ears
- Muscle cramps
- Pains in joints and muscles
- Abnormal liver function
- Increased blood potassium levels
- Impaired kidney function
- Inflammation of small blood vessels mainly affecting the skin (a condition known as leukocytoclastic vasculitis).

Uncertain cases of jaundice (yellowing of the skin and/or whiteness of the eyes) have also been reported.

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 TABLETS

Keep out of the reach and sight of children.

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

Do not store above 25°C.

Store in the original package to protect from light.

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

6. FURTHER INFORMATION

What Irbesartan Tablets contain

The active substance is Irbesartan.

Each tablet of Irbesartan Tablets 25 mg contains 25 mg Irbesartan.

Each tablet of Irbesartan Tablets 50 mg contains 50 mg Irbesartan.

Each tablet of Irbesartan Tablets 150 mg contains 150 mg Irbesartan.

The tablet of Irbesartan Tablets 300 mg contains 300 mg Irbesartan.

The other ingredients are Cellulose microcrystalline, Lactose monohydrate, Croscarmellose Sodium (Type A), Hydroxypropylcellulose, Talc (E553), Sodium starch. Furthermore, Povidone hydroxyethyl, Titanium dioxide (E171) and Macrogol 3350.

What Irbesartan Tablets look like and contents of the pack

Irbesartan Tablets 75 mg film-coated tablets are white, approximately 9.0 x 9.0 mm oval shaped coated tablet with '15' on one side and '5' on the other side.

Irbesartan Tablets 150 mg film-coated tablets are white, approximately 6.5 x 12.5 mm oval shaped coated tablet with 'IS150' on one side and '5' on the other side.

Irbesartan Tablets 300 mg film-coated tablets are white, approximately 8.0 x 15.5 mm oval shaped coated tablet with 'IS300' on one side and '+3' on the other side.

Irbesartan Tablets are supplied in blisters of 14, 28, 30, 56, 60, 90 or 98 film-coated tablets packed in an outer carton.

Not all pack sizes may be marketed.

Marketing Authorisation Holder:

Arrow AsP, Sankt Peders Stræde 2, 4000 Roskilde, Denmark.

Manufacturer:

Arrow Pharma Malta, HF02, Hal Far Industrial Estate, Birkirkara B801 06, Malta.

This leaflet was last approved on 03/2012.
Module 4
Labelling
### Blister:

<table>
<thead>
<tr>
<th>MON</th>
<th>TUE</th>
<th>WED</th>
<th>THU</th>
<th>FRI</th>
<th>SAT</th>
<th>SUN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Irbesartan 75mg Film-coated Tablets</strong> (irbesartan) Arrow ApS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MON</th>
<th>TUE</th>
<th>WED</th>
<th>THU</th>
<th>FRI</th>
<th>SAT</th>
<th>SUN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Irbesartan 75mg Film-coated Tablets</strong> (irbesartan) Arrow ApS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MON</th>
<th>TUE</th>
<th>WED</th>
<th>THU</th>
<th>FRI</th>
<th>SAT</th>
<th>SUN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Irbesartan 75mg Film-coated Tablets</strong> (irbesartan) Arrow ApS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MON</th>
<th>TUE</th>
<th>WED</th>
<th>THU</th>
<th>FRI</th>
<th>SAT</th>
<th>SUN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Irbesartan 75mg Film-coated Tablets</strong> (irbesartan) Arrow ApS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PAR Irbesartan 75mg, 150mg and 300mg Film-coated Tablets

Carton:

For oral use. Read the package leaflet before use.
Contains lactose monohydrate.
See leaflet for further information.
Do not store above 25°C. Store in the original
package in order to protect from light.
Keep out of the reach and sight of children.

Irbesartan 150mg Film-coated Tablets
28 film-coated tablets

Irbesartan 150mg Film-coated Tablets (irbesartan)
28 film-coated tablets

Each film-coated tablet contains 150mg of irbesartan.

Irbesartan 150mg Film-coated Tablets
28 film-coated tablets
Blister:

**Irbesartan 150mg Film-coated Tablets**
(irbesartan) Arrow ApS

**Irbesartan 150mg Film-coated Tablets**
(irbesartan) Arrow ApS

**Irbesartan 150mg Film-coated Tablets**
(irbesartan) Arrow ApS

**Irbesartan 150mg Film-coated Tablets**
(irbesartan) Arrow ApS

**Irbesartan 150mg Film-coated Tablets**
(irbesartan) Arrow ApS

**Irbesartan 150mg Film-coated Tablets**
(irbesartan) Arrow ApS
For oral use. Read the package leaflet before use.
Contains lactose monohydrate.
See leaflet for further information.
Do not store above 25°C. Store in the original package in order to protect from light.
Keep out of the reach and sight of children.

PL 3276/0004
Marketing Authorisation Holder:
Arrow Aps, Skovlunde Strandvejen 1, 1,
DK-4000 Roskilde, Denmark

Irbesartan 300mg Film-coated Tablets
28 film-coated tablets

Each film-coated tablet contains 300mg of irbesartan.
Par irbesartan 75mg, 150mg and 300mg film-coated tablets.

Blister:
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Irbesartan 75mg, 150mg and 300mg Film-coated Tablets (PL 33786/0002-4; UK/H/3094/001-3/DC) could be approved. These applications were submitted via the decentralised procedure, with the UK as Reference Member State (RMS) and Czech Republic, Germany, Denmark, Greece, Spain, Finland, France, Ireland, Italy, Malta, Netherlands, Norway and Sweden as Concerned Member State (CMS). These products are prescription-only medicines (POM).

Irbesartan 75mg, 150mg and 300mg Film-coated Tablets are indicated for the:
- 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 of SmPC).

These are abridged applications submitted under Article 10(1) of Directive 2001/83/EC as amended, cross-referring to Aprovel 75 mg, 150 mg and 300 mg tablets (Sanofi Pharma Bristol-Meyers Squibb SNC), which were first authorised using the Centralised procedure in August 1997.

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.

No new non-clinical studies were conducted, which is acceptable given that the products are intended to be generic versions of the originator products that have been licensed for over 10 years.

One bioequivalence study (single dose) was submitted to support these applications, comparing the test product Irbesartan 300mg Film-coated Tablets (Arrow ApS) with the reference product Aprovel 300 mg tablets (Sanofi Pharma Bristol-Meyers Squibb SNC).

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications were for products that are intended to be generic versions of the originator products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.
The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 21 March 2012. After a subsequent national phase, the licences were granted in the UK on 24 April 2012.
## ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Irbesartan 75mg Film-coated Tablets  
Irbesartan 150mg Film-coated Tablets  
Irbesartan 300mg Film-coated Tablets |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Irbesartan</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Angiotensin II antagonists, plain (C09C A04)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>75 mg, 150 mg and 300 mg film-coated tablets</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/3094/001-3/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Concerned Member State</td>
<td>Czech Republic, Germany, Denmark, Greece, Spain, Finland, France, Ireland, Italy, Malta, Netherlands, Norway, Sweden.</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 33786/0002-4</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Arrow ApS, Sankt Peders Stræde 2,1., 4000 Roskilde, Denmark.</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Irbesartan
Chemical name: 2-Butyl-3-[[2’-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-
diazaspiro[4.4]non-1-en-4-one

Structure:

![Structure of Irbesartan]

Molecular formula: \( C_{25}H_{28}N_6O \)
Molecular mass: 428.5
Appearance: Irbesartan is a white to off-white crystalline powder.
Solubility: It is slightly soluble in ethanol (96%), chloroform and methylene chloride and practically insoluble in water.

Irbesartan is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose, lactose monohydrate, crospovidone (Type A), hydroxypropylcellulose, talc (E553b), sodium stearyl fumarate and Opadry II 8F18378 White [consisting of polyvinyl alcohol, partially hydrolysed titanium dioxide (E171), macrogol 3350 and talc (E553b)]
All excipients comply with their respective European Pharmacopoeia monographs with the exception of Opadry II 8F18378 White which complies with suitable in-house specifications. Satisfactory certificates of analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the lactose is sourced from healthy animals under the same conditions as milk for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of these products.

**Pharmaceutical Development**

The objective of the development programme was to formulate stable, robust tablets containing 75 mg, 150 mg or 300 mg irbesartan, which could be considered generic medicinal products of Aprovel 75 mg, 150 mg and 300 mg tablets (Sanofi Pharma Bristol-Meyers Squibb SNC).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

**Manufacturing Process**

Satisfactory batch formulae have been provided for the manufacture of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale and has shown satisfactory results.

**Finished Product Specification**

The proposed finished product specifications are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided, which comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

**Container-Closure System**

All strengths of the finished product are packaged in polyvinylchloride/polyvinylidene chloride/ aluminium foil blister strips in pack sizes of 14, 28, 30, 56, 84, 90, or 98 film-coated tablets.

It has been stated that not all pack sizes may be marketed, however, the Marketing Authorisation Holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

**Stability of the product**

Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 15 months with the storage conditions ‘Do not store above 25°C. Store in the original package in order to protect from light.’
Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, PIL and labels are acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. 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 it contains.

Marketing Authorisation Application (MAA) form
The MAA forms are satisfactory.

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

Conclusion
There are no objections to the approval of these products from a pharmaceutical viewpoint.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of irbesartan are well-known, no new non-clinical studies are required and none have been provided.

The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant pharmacology and toxicology.

Since Irbesartan 75mg, 150mg and 300mg Film-coated Tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment (ERA) is therefore not deemed necessary.

There are no objections to the approval of these products from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS
Pharmacokinetics
In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open label, randomised, single-dose, two-period, two-sequence, two treatment, crossover study to compare the pharmacokinetics of the test product Irbesartan 300mg Film-coated Tablets (Arrow ApS) versus the reference product Aprovel 300 mg tablets (Sanofi Pharma Bristol-Meyers Squibb SNC) in healthy adult volunteers under fasted conditions.
All volunteers received a single oral dose of either the test or reference product as a 1 x 300 mg tablet administered after an overnight fast of at least 10 hours. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 48 hours post dose. The washout period between treatment periods was at least 7 days.

The pharmacokinetic results for irbesartan are presented below (log-transformed values; least square mean, ratios of geometric mean and 90% confidence intervals):

**Analyte: Irbesartan (N = 39)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TRT</th>
<th>Means</th>
<th>90% CI</th>
<th>Intra-Sub CV(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Arithmetic (CV%)</td>
<td>Geometric</td>
<td>Contrast</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;inf&lt;/sub&gt;</td>
<td>A</td>
<td>18605.83 (29)</td>
<td>17931.85</td>
<td>A vs. B</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>18466.07 (33)</td>
<td>17601.73</td>
<td>-</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt;</td>
<td>A</td>
<td>19762.00 (34)</td>
<td>-</td>
<td>A vs. B</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>10487.55 (36)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>A</td>
<td>3613.50 (32)</td>
<td>3471.57</td>
<td>A vs. B</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>3726.41 (38)</td>
<td>3514.83</td>
<td>-</td>
</tr>
</tbody>
</table>

The 90% confidence intervals for AUC and C<sub>max</sub> for test versus reference product for irbesartan are within predefined acceptance criteria specified in "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev 1/, Corr). Thus, the data support the claim that the test product is bioequivalent to the reference product.

As the 75 mg, 150 mg and 300 mg strengths of the product meet the criteria specified in "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev 1/, Corr), the results and conclusions of the bioequivalence study on the 300 mg strength can be extrapolated to the 75 mg and 150 mg strengths.

**Pharmacodynamics**
No new pharmacodynamic data were submitted and none were required for these applications.

**Efficacy**
No new efficacy data were submitted and none were required for these applications.

**Safety**
With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for these applications. No new or unexpected safety issues were highlighted by the bioequivalence data.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**
The SmPCs, PIL and labels are acceptable. The SmPCs are consistent with that for the originator products. The PIL is consistent with the SmPCs and in line with current guidelines. The labelling is in-line with current guidelines.

**Clinical Expert Report**
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Pharmacovigilance System and Risk Management Plan**

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for these products.

**Conclusion**

There are no objections to the approval of these products from a clinical viewpoint.

**IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT**

**QUALITY**

The quality characteristics of Irbesartan 75mg, 150mg 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.

**NON-CLINICAL**

No new non-clinical data were submitted and none are required for applications of this type. The pharmacodynamic, pharmacokinetic and toxicological properties of irbesartan are well-known.

**EFFICACY**

With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type. Bioequivalence has been demonstrated between the applicant’s Irbesartan 300mg Film-coated Tablets and its respective reference product Aprovel 300 mg tablets (Sanofi Pharma Bristol-Meyers Squibb SNC). As the 75 mg, 150 mg and 300 mg strengths of the product meet the biowaiver criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/, Corr), the results and conclusions of the bioequivalence study on the 300 mg strength can be extrapolated to the 75 mg and 150 mg strengths.

**SAFETY**

With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type. As the safety profile of irbesartan is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

**PRODUCT LITERATURE**

The SmPCs, PIL and labelling are satisfactory and consistent with that for the reference products, where appropriate, in line with current guidelines.

**BENEFIT-RISK ASSESSMENT**

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s
products and the originator products are interchangeable. Extensive clinical experience with irbesartan is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Module 6

**STEPS TAKEN AFTER INITIAL PROCEDURE - 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>