**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Irbesartan BMS 75 mg tablets.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 75 mg of irbesartan.

Excipient: 15.37 mg of lactose monohydrate per tablet.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet.
White to off-white, biconvex, and oval-shaped with a heart debossed on one side and the number 2771 engraved on the other side.



## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

### 4.2 Posology and method of administration

The usual recommended initial and maintenance dose is 150 mg once daily, with or without food. Irbesartan BMS 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 BMS 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 BMS (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 BMS in hypertensive type 2 diabetic patients is based on studies where irbesartan was used in addition to other antihypertensive agents, as needed, to reach target blood pressure (see section 5.1).

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

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

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

Paediatric patients: irbesartan is not recommended for use in children and adolescents due to insufficient data on safety and efficacy (see sections 4.8, 5.1 and 5.2).

## 4.3 Contraindications

Hypersensitivity to the active substance, or to any of the excipients (see section 6.1).
Second and third 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 BMS.

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 BMS, a similar effect should be anticipated with angiotensin-II receptor antagonists.

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

**4.5 Interaction with other medicinal products and other forms of interaction**

Diuretics and other antihypertensive agents: other antihypertensive agents may increase the hypotensive effects of irbesartan; however Irbesartan BMS 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 BMS (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 coadministration of irbesartan.

## 4.6 Pregnancy and lactation

Pregnancy:

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

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Antagonists (AIIRAs), similar risks may exist for this class of drugs. Unless continued 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 BMS during breast-feeding, Irbesartan BMS is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

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

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

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

The frequency of adverse reactions listed below is defined using the following convention:

very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

*Investigations:*

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

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

*Cardiac disorders:*

Uncommon: tachycardia

*Nervous system disorders:*

Common: dizziness, orthostatic dizziness*

*Respiratory, thoracic and mediastinal disorders:*

Uncommon: cough

*Gastrointestinal disorders:*

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

*Musculoskeletal and connective tissue disorders:*

Common: musculoskeletal pain*

*Vascular disorders:*

Common: orthostatic hypotension*
Uncommon: flushing

*General disorders and administration site conditions:*

Common: fatigue
Uncommon: chest pain

*Reproductive system and breast disorders:*

Uncommon: sexual dysfunction

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

*Nervous system disorders:*

Headache

*Ear and labyrinth disorders:*

Tinnitus

*Gastrointestinal disorders:*
Dysgeusia

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

*Skin and subcutaneous tissue disorders:*
Leukocytoclastic vasculitis

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

*Metabolism and nutrition disorders:*
Hyperkalaemia

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

*Hepato-biliary disorders:*
Hepatitis, abnormal liver function

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

### 4.9 Overdose

Experience in adults exposed to doses of up to 900 mg/day for 8 weeks revealed no toxicity. The most likely manifestations of 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 BMS. 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 $AT_1$) antagonist. It is expected to block all actions of angiotensin-II mediated by the $AT_1$ receptor, regardless of the source or route of synthesis of angiotensin-II. The selective antagonism of the angiotensin-II ($AT_1$) receptors results in increases in plasma renin levels and angiotensin-II levels, and a decrease in plasma aldosterone concentration. Serum potassium levels are not significantly affected by irbesartan alone at the recommended doses. Irbesartan does not inhibit ACE (kininase-II), an enzyme which generates angiotensin-II and also degrades bradykinin into inactive metabolites. Irbesartan does not require metabolic activation for its activity.

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 BMS 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 BMS is not influenced by age or gender. As is the case with other medicinal products that affect the renin-angiotensin system, black hypertensive patients have notably less response to irbesartan monotherapy. When irbesartan is administered concomitantly with a low dose of hydrochlorothiazide (e.g. 12.5 mg daily), the antihypertensive response in black patients approaches that of white patients.
There is no clinically important effect on serum uric acid or urinary uric acid secretion.

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

Hypertension and type 2 diabetes with renal disease
The "Irbesartan Diabetic Nephropathy Trial (IDNT)" shows that irbesartan decreases the progression of renal disease in patients with chronic renal insufficiency and overt proteinuria. IDNT was a double blind, controlled, morbidity and mortality trial comparing Irbesartan BMS, 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 BMS 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 BMS, from 2.5 mg to 10 mg amlodipine, or placebo as tolerated. Patients in all treatment groups typically received between 2 and 4 antihypertensive agents (e.g., diuretics, beta blockers, alpha blockers) to reach a predefined blood pressure goal of ≤ 135/85 mmHg or a 10 mmHg reduction in systolic pressure if baseline was > 160 mmHg. Sixty per cent (60%) of patients in the placebo group reached this target blood pressure whereas this figure was 76% and 78% in the irbesartan and amlodipine groups respectively. Irbesartan significantly reduced the relative risk in the primary combined endpoint of doubling serum creatinine, end-stage renal disease (ESRD) or all-cause mortality. Approximately 33% of patients in the irbesartan group reached the primary renal composite endpoint compared to 39% and 41% in the placebo and amlodipine groups [20% relative risk reduction versus placebo (p = 0.024) and 23% relative risk reduction compared to amlodipine (p = 0.006)]. When the individual components of the primary endpoint were

analysed, no effect in all cause mortality was observed, while a positive trend in the reduction in ESRD and a significant reduction in doubling of serum creatinine were observed.

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

The study of the "Effects of Irbesartan on Microalbuminuria in Hypertensive Patients with type 2 Diabetes Mellitus (IRMA 2)" shows that irbesartan 300 mg delays progression to overt proteinuria in patients with microalbuminuria. IRMA 2 was a placebo-controlled double blind morbidity study in 590 patients with type 2 diabetes, microalbuminuria (30-300 mg/day) and normal renal function (serum creatinine ≤ 1.5 mg/dl in males and < 1.1 mg/dl in females). The study examined the long-term effects (2 years) of Irbesartan BMS 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 BMS 300 mg group (34%) than in the placebo group (21%).



## 5.2 Pharmacokinetic properties

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

Irbesartan exhibits linear and dose proportional pharmacokinetics over the dose range of 10 to 600 mg. A less than proportional increase in oral absorption at doses beyond 600 mg (twice the maximal recommended dose) was observed; the mechanism for this is unknown. Peak plasma concentrations are attained at 1.5-2 hours after oral administration. The total body and renal clearance are 157-176 and 3-3.5 ml/min, respectively. The terminal elimination half-life of irbesartan is 11-15 hours. Steady-state plasma concentrations are attained within 3 days after initiation of a once-daily dosing regimen. Limited accumulation of irbesartan (< 20%) is observed in plasma upon repeated once-daily dosing. In a study, somewhat higher plasma concentrations of irbesartan were observed in female hypertensive patients. However, there was no difference in the half-life and accumulation of irbesartan. No dosage adjustment is necessary in female patients. Irbesartan AUC and $C_{max}$ values were also somewhat greater in elderly subjects (≥ 65 years) than those of young subjects (18-40 years).

However the terminal half-life was not significantly altered. No dosage adjustment is necessary in elderly patients.

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

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

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

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



### 5.3 Preclinical safety data

There was no evidence of abnormal systemic or target organ toxicity at clinically relevant doses. In non-clinical safety studies, high doses of irbesartan (≥ 250 mg/kg/day in rats and ≥ 100 mg/kg/day in macaques) caused a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit). At very high doses (≥ 500 mg/kg/day) degenerative changes in the kidney (such as interstitial nephritis, tubular distension, basophilic tubules, increased plasma concentrations of urea and creatinine) were induced by irbesartan in the rat and the macaque and are considered secondary to the hypotensive effects of the medicinal product which led to decreased renal perfusion. Furthermore, irbesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells (in rats at ≥ 90 mg/kg/day, in macaques at ≥ 10 mg/kg/day). All of these changes were considered to be caused by the pharmacological action of irbesartan. For therapeutic doses of irbesartan in humans, the hyperplasia/ hypertrophy of the renal juxtaglomerular cells does not appear to have any relevance.

There was no evidence of mutagenicity, clastogenicity or carcinogenicity.

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

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Microcrystalline cellulose
Croscarmellose sodium
Lactose monohydrate
Magnesium stearate
Colloidal hydrated silica
Pregelatinised maize starch
Poloxamer 188

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Do not store above 30°C.

### 6.5 Nature and contents of container

Cartons of 14 tablets: 1 blister card of 14 tablets in PVC/PVDC/Aluminium blisters.
Cartons of 28 tablets: 2 blister cards of 14 tablets in PVC/PVDC/Aluminium blisters.
Cartons of 56 tablets: 4 blister cards of 14 tablets in PVC/PVDC/Aluminium blisters.
Cartons of 98 tablets: 7 blister cards of 14 tablets in PVC/PVDC/Aluminium blisters.
Cartons of 56 x 1 tablet; 7 blister cards of 8 x 1 tablet each in PVC/PVDC/Aluminium perforated unit dose blisters.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

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

## 7. MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH - United Kingdom

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/06/375/001-005

## 9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 January 2007
Date of latest renewal:

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

## 1. NAME OF THE MEDICINAL PRODUCT

Irbesartan BMS 150 mg tablets.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 150 mg of irbesartan.

Excipient: 30.75 mg of lactose monohydrate per tablet.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet.
White to off-white, biconvex, and oval-shaped with a heart debossed on one side and the number 2772 engraved on the other side.



## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

### 4.2 Posology and method of administration

The usual recommended initial and maintenance dose is 150 mg once daily, with or without food. Irbesartan BMS 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 BMS 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 BMS (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 BMS in hypertensive type 2 diabetic patients is based on studies where irbesartan was used in addition to other antihypertensive agents, as needed, to reach target blood pressure (see section 5.1).

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

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

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

Paediatric patients: irbesartan is not recommended for use in children and adolescents due to insufficient data on safety and efficacy (see sections 4.8, 5.1 and 5.2).

## 4.3 Contraindications

Hypersensitivity to the active substance, or to any of the excipients (see section 6.1).
Second and third 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 BMS.

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 BMS, a similar effect should be anticipated with angiotensin-II receptor antagonists.

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

**4.5 Interaction with other medicinal products and other forms of interaction**

Diuretics and other antihypertensive agents: other antihypertensive agents may increase the hypotensive effects of irbesartan; however Irbesartan BMS 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 BMS (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 coadministration of irbesartan.

## 4.6 Pregnancy and lactation

Pregnancy:

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

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Antagonists (AIIRAs), similar risks may exist for this class of drugs. Unless continued 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 BMS during breast-feeding, Irbesartan BMS is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

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

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

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

The frequency of adverse reactions listed below is defined using the following convention:

very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

*Investigations:*

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

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

*Cardiac disorders:*

Uncommon: tachycardia

*Nervous system disorders:*

Common: dizziness, orthostatic dizziness*

*Respiratory, thoracic and mediastinal disorders:*

Uncommon: cough

*Gastrointestinal disorders:*

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

*Musculoskeletal and connective tissue disorders:*

Common: musculoskeletal pain*

*Vascular disorders:*

Common: orthostatic hypotension*
Uncommon: flushing

*General disorders and administration site conditions:*

Common: fatigue
Uncommon: chest pain

*Reproductive system and breast disorders:*

Uncommon: sexual dysfunction

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

*Nervous system disorders:*

Headache

*Ear and labyrinth disorders:*

Tinnitus

*Gastrointestinal disorders:*
Dysgeusia

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

*Skin and subcutaneous tissue disorders:*
Leukocytoclastic vasculitis

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

*Metabolism and nutrition disorders:*
Hyperkalaemia

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

*Hepato-biliary disorders:*
Hepatitis, abnormal liver function

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

### 4.9 Overdose

Experience in adults exposed to doses of up to 900 mg/day for 8 weeks revealed no toxicity. The most likely manifestations of 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 BMS. 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 $AT_1$) antagonist. It is expected to block all actions of angiotensin-II mediated by the $AT_1$ receptor, regardless of the source or route of synthesis of angiotensin-II. The selective antagonism of the angiotensin-II ($AT_1$) receptors results in increases in plasma renin levels and angiotensin-II levels, and a decrease in plasma aldosterone concentration. Serum potassium levels are not significantly affected by irbesartan alone at the recommended doses. Irbesartan does not inhibit ACE (kininase-II), an enzyme which generates angiotensin-II and also degrades bradykinin into inactive metabolites. Irbesartan does not require metabolic activation for its activity.

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 BMS 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 BMS is not influenced by age or gender. As is the case with other medicinal products that affect the renin-angiotensin system, black hypertensive patients have notably less response to irbesartan monotherapy. When irbesartan is administered concomitantly with a low dose of hydrochlorothiazide (e.g. 12.5 mg daily), the antihypertensive response in black patients approaches that of white patients.
There is no clinically important effect on serum uric acid or urinary uric acid secretion.

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

Hypertension and type 2 diabetes with renal disease
The “Irbesartan Diabetic Nephropathy Trial (IDNT)” shows that irbesartan decreases the progression of renal disease in patients with chronic renal insufficiency and overt proteinuria. IDNT was a double blind, controlled, morbidity and mortality trial comparing Irbesartan BMS, 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 BMS 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 BMS, from 2.5 mg to 10 mg amlodipine, or placebo as tolerated. Patients in all treatment groups typically received between 2 and 4 antihypertensive agents (e.g., diuretics, beta blockers, alpha blockers) to reach a predefined blood pressure goal of ≤ 135/85 mmHg or a 10 mmHg reduction in systolic pressure if baseline was > 160 mmHg. Sixty per cent (60%) of patients in the placebo group reached this target blood pressure whereas this figure was 76% and 78% in the irbesartan and amlodipine groups respectively. Irbesartan significantly reduced the relative risk in the primary combined endpoint of doubling serum creatinine, end-stage renal disease (ESRD) or all-cause mortality. Approximately 33% of patients in the irbesartan group reached the primary renal composite endpoint compared to 39% and 41% in the placebo and amlodipine groups [20% relative risk reduction versus placebo (p = 0.024) and 23% relative risk reduction compared to amlodipine (p = 0.006)]. When the individual components of the primary endpoint were

analysed, no effect in all cause mortality was observed, while a positive trend in the reduction in ESRD and a significant reduction in doubling of serum creatinine were observed.

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

The study of the "Effects of Irbesartan on Microalbuminuria in Hypertensive Patients with type 2 Diabetes Mellitus (IRMA 2)" shows that irbesartan 300 mg delays progression to overt proteinuria in patients with microalbuminuria. IRMA 2 was a placebo-controlled double blind morbidity study in 590 patients with type 2 diabetes, microalbuminuria (30-300 mg/day) and normal renal function (serum creatinine ≤ 1.5 mg/dl in males and < 1.1 mg/dl in females). The study examined the long-term effects (2 years) of Irbesartan BMS 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 BMS 300 mg group (34%) than in the placebo group (21%).



## 5.2 Pharmacokinetic properties

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

Irbesartan exhibits linear and dose proportional pharmacokinetics over the dose range of 10 to 600 mg. A less than proportional increase in oral absorption at doses beyond 600 mg (twice the maximal recommended dose) was observed; the mechanism for this is unknown. Peak plasma concentrations are attained at 1.5-2 hours after oral administration. The total body and renal clearance are 157-176 and 3-3.5 ml/min, respectively. The terminal elimination half-life of irbesartan is 11-15 hours. Steady-state plasma concentrations are attained within 3 days after initiation of a once-daily dosing regimen. Limited accumulation of irbesartan (< 20%) is observed in plasma upon repeated once-daily dosing. In a study, somewhat higher plasma concentrations of irbesartan were observed in female hypertensive patients. However, there was no difference in the half-life and accumulation of irbesartan. No dosage adjustment is necessary in female patients. Irbesartan AUC and $C_{max}$ values were also somewhat greater in elderly subjects (≥ 65 years) than those of young subjects (18-40 years).

However the terminal half-life was not significantly altered. No dosage adjustment is necessary in elderly patients.

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

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

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

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



### 5.3 Preclinical safety data

There was no evidence of abnormal systemic or target organ toxicity at clinically relevant doses. In non-clinical safety studies, high doses of irbesartan (≥ 250 mg/kg/day in rats and ≥ 100 mg/kg/day in macaques) caused a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit). At very high doses (≥ 500 mg/kg/day) degenerative changes in the kidney (such as interstitial nephritis, tubular distension, basophilic tubules, increased plasma concentrations of urea and creatinine) were induced by irbesartan in the rat and the macaque and are considered secondary to the hypotensive effects of the medicinal product which led to decreased renal perfusion. Furthermore, irbesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells (in rats at ≥ 90 mg/kg/day, in macaques at ≥ 10 mg/kg/day). All of these changes were considered to be caused by the pharmacological action of irbesartan. For therapeutic doses of irbesartan in humans, the hyperplasia/ hypertrophy of the renal juxtaglomerular cells does not appear to have any relevance.

There was no evidence of mutagenicity, clastogenicity or carcinogenicity.

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

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Microcrystalline cellulose
Croscarmellose sodium
Lactose monohydrate
Magnesium stearate
Colloidal hydrated silica
Pregelatinised maize starch
Poloxamer 188

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Do not store above 30°C.

### 6.5 Nature and contents of container

Cartons of 14 tablets: 1 blister card of 14 tablets in PVC/PVDC/Aluminium blisters.
Cartons of 28 tablets: 2 blister cards of 14 tablets in PVC/PVDC/Aluminium blisters.
Cartons of 56 tablets: 4 blister cards of 14 tablets in PVC/PVDC/Aluminium blisters.
Cartons of 98 tablets: 7 blister cards of 14 tablets in PVC/PVDC/Aluminium blisters.
Cartons of 56 x 1 tablet; 7 blister cards of 8 x 1 tablet each in PVC/PVDC/Aluminium perforated unit dose blisters.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

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

## 7. MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH - United Kingdom

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/06/375/006-010

## 9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 January 2007
Date of latest renewal:

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

## 1. NAME OF THE MEDICINAL PRODUCT

Irbesartan BMS 300 mg tablets.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 300 mg of irbesartan.

Excipient: 61.50 mg of lactose monohydrate per tablet.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet.
White to off-white, biconvex, and oval-shaped with a heart debossed on one side and the number 2773 engraved on the other side.



## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

### 4.2 Posology and method of administration

The usual recommended initial and maintenance dose is 150 mg once daily, with or without food. Irbesartan BMS 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 BMS 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 BMS (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 BMS in hypertensive type 2 diabetic patients is based on studies where irbesartan was used in addition to other antihypertensive agents, as needed, to reach target blood pressure (see section 5.1).

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

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

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

Paediatric patients: irbesartan is not recommended for use in children and adolescents due to insufficient data on safety and efficacy (see sections 4.8, 5.1 and 5.2).

## 4.3 Contraindications

Hypersensitivity to the active substance, or to any of the excipients (see section 6.1).
Second and third 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 BMS.

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 BMS, a similar effect should be anticipated with angiotensin-II receptor antagonists.

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

**4.5 Interaction with other medicinal products and other forms of interaction**

Diuretics and other antihypertensive agents: other antihypertensive agents may increase the hypotensive effects of irbesartan; however Irbesartan BMS 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 BMS (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 coadministration of irbesartan.

## 4.6 Pregnancy and lactation

Pregnancy:

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

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Antagonists (AIIRAs), similar risks may exist for this class of drugs. Unless continued 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 BMS during breast-feeding, Irbesartan BMS is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

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

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

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

The frequency of adverse reactions listed below is defined using the following convention:

very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

*Investigations:*

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

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

*Cardiac disorders:*

Uncommon: tachycardia

*Nervous system disorders:*

Common: dizziness, orthostatic dizziness*

*Respiratory, thoracic and mediastinal disorders:*

Uncommon: cough

*Gastrointestinal disorders:*

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

*Musculoskeletal and connective tissue disorders:*

Common: musculoskeletal pain*

*Vascular disorders:*

Common: orthostatic hypotension*
Uncommon: flushing

*General disorders and administration site conditions:*

Common: fatigue
Uncommon: chest pain

*Reproductive system and breast disorders:*

Uncommon: sexual dysfunction

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

*Nervous system disorders:*

Headache

*Ear and labyrinth disorders:*

Tinnitus

*Gastrointestinal disorders:*
Dysgeusia

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

*Skin and subcutaneous tissue disorders:*
Leukocytoclastic vasculitis

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

*Metabolism and nutrition disorders:*
Hyperkalaemia

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

*Hepato-biliary disorders:*
Hepatitis, abnormal liver function

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

### 4.9 Overdose

Experience in adults exposed to doses of up to 900 mg/day for 8 weeks revealed no toxicity. The most likely manifestations of 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 BMS. 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 $AT_1$) antagonist. It is expected to block all actions of angiotensin-II mediated by the $AT_1$ receptor, regardless of the source or route of synthesis of angiotensin-II. The selective antagonism of the angiotensin-II ($AT_1$) receptors results in increases in plasma renin levels and angiotensin-II levels, and a decrease in plasma aldosterone concentration. Serum potassium levels are not significantly affected by irbesartan alone at the recommended doses. Irbesartan does not inhibit ACE (kininase-II), an enzyme which generates angiotensin-II and also degrades bradykinin into inactive metabolites. Irbesartan does not require metabolic activation for its activity.

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 BMS 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 BMS is not influenced by age or gender. As is the case with other medicinal products that affect the renin-angiotensin system, black hypertensive patients have notably less response to irbesartan monotherapy. When irbesartan is administered concomitantly with a low dose of hydrochlorothiazide (e.g. 12.5 mg daily), the antihypertensive response in black patients approaches that of white patients.
There is no clinically important effect on serum uric acid or urinary uric acid secretion.

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

Hypertension and type 2 diabetes with renal disease
The “Irbesartan Diabetic Nephropathy Trial (IDNT)” shows that irbesartan decreases the progression of renal disease in patients with chronic renal insufficiency and overt proteinuria. IDNT was a double blind, controlled, morbidity and mortality trial comparing Irbesartan BMS, 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 BMS 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 BMS, from 2.5 mg to 10 mg amlodipine, or placebo as tolerated. Patients in all treatment groups typically received between 2 and 4 antihypertensive agents (e.g., diuretics, beta blockers, alpha blockers) to reach a predefined blood pressure goal of ≤ 135/85 mmHg or a 10 mmHg reduction in systolic pressure if baseline was > 160 mmHg. Sixty per cent (60%) of patients in the placebo group reached this target blood pressure whereas this figure was 76% and 78% in the irbesartan and amlodipine groups respectively. Irbesartan significantly reduced the relative risk in the primary combined endpoint of doubling serum creatinine, end-stage renal disease (ESRD) or all-cause mortality. Approximately 33% of patients in the irbesartan group reached the primary renal composite endpoint compared to 39% and 41% in the placebo and amlodipine groups [20% relative risk reduction versus placebo (p = 0.024) and 23% relative risk reduction compared to amlodipine (p = 0.006)]. When the individual components of the primary endpoint were

analysed, no effect in all cause mortality was observed, while a positive trend in the reduction in ESRD and a significant reduction in doubling of serum creatinine were observed.

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

The study of the "Effects of Irbesartan on Microalbuminuria in Hypertensive Patients with type 2 Diabetes Mellitus (IRMA 2)" shows that irbesartan 300 mg delays progression to overt proteinuria in patients with microalbuminuria. IRMA 2 was a placebo-controlled double blind morbidity study in 590 patients with type 2 diabetes, microalbuminuria (30-300 mg/day) and normal renal function (serum creatinine ≤ 1.5 mg/dl in males and < 1.1 mg/dl in females). The study examined the long-term effects (2 years) of Irbesartan BMS 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 BMS 300 mg group (34%) than in the placebo group (21%).



## 5.2 Pharmacokinetic properties

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

Irbesartan exhibits linear and dose proportional pharmacokinetics over the dose range of 10 to 600 mg. A less than proportional increase in oral absorption at doses beyond 600 mg (twice the maximal recommended dose) was observed; the mechanism for this is unknown. Peak plasma concentrations are attained at 1.5-2 hours after oral administration. The total body and renal clearance are 157-176 and 3-3.5 ml/min, respectively. The terminal elimination half-life of irbesartan is 11-15 hours. Steady-state plasma concentrations are attained within 3 days after initiation of a once-daily dosing regimen. Limited accumulation of irbesartan (< 20%) is observed in plasma upon repeated once-daily dosing. In a study, somewhat higher plasma concentrations of irbesartan were observed in female hypertensive patients. However, there was no difference in the half-life and accumulation of irbesartan. No dosage adjustment is necessary in female patients. Irbesartan AUC and $C_{max}$ values were also somewhat greater in elderly subjects (≥ 65 years) than those of young subjects (18-40 years).

However the terminal half-life was not significantly altered. No dosage adjustment is necessary in elderly patients.

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

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

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

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



### 5.3 Preclinical safety data

There was no evidence of abnormal systemic or target organ toxicity at clinically relevant doses. In non-clinical safety studies, high doses of irbesartan (≥ 250 mg/kg/day in rats and ≥ 100 mg/kg/day in macaques) caused a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit). At very high doses (≥ 500 mg/kg/day) degenerative changes in the kidney (such as interstitial nephritis, tubular distension, basophilic tubules, increased plasma concentrations of urea and creatinine) were induced by irbesartan in the rat and the macaque and are considered secondary to the hypotensive effects of the medicinal product which led to decreased renal perfusion. Furthermore, irbesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells (in rats at ≥ 90 mg/kg/day, in macaques at ≥ 10 mg/kg/day). All of these changes were considered to be caused by the pharmacological action of irbesartan. For therapeutic doses of irbesartan in humans, the hyperplasia/ hypertrophy of the renal juxtaglomerular cells does not appear to have any relevance.

There was no evidence of mutagenicity, clastogenicity or carcinogenicity.

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

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Microcrystalline cellulose
Croscarmellose sodium
Lactose monohydrate
Magnesium stearate
Colloidal hydrated silica
Pregelatinised maize starch
Poloxamer 188

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Do not store above 30°C.

### 6.5 Nature and contents of container

Cartons of 14 tablets: 1 blister card of 14 tablets in PVC/PVDC/Aluminium blisters.
Cartons of 28 tablets: 2 blister cards of 14 tablets in PVC/PVDC/Aluminium blisters.
Cartons of 56 tablets: 4 blister cards of 14 tablets in PVC/PVDC/Aluminium blisters.
Cartons of 98 tablets: 7 blister cards of 14 tablets in PVC/PVDC/Aluminium blisters.
Cartons of 56 x 1 tablet; 7 blister cards of 8 x 1 tablet each in PVC/PVDC/Aluminium perforated unit dose blisters.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

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

## 7. MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH - United Kingdom

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/06/375/011-015

## 9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 January 2007
Date of latest renewal:

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

## 1. NAME OF THE MEDICINAL PRODUCT

Irbesartan BMS 75 mg film-coated tablets.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 75 mg of irbesartan.

Excipient: 25.50 mg of lactose monohydrate per film-coated tablet.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.
White to off-white, biconvex, and oval-shaped with a heart debossed on one side and the number 2871 engraved on the other side.



## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

### 4.2 Posology and method of administration

The usual recommended initial and maintenance dose is 150 mg once daily, with or without food. Irbesartan BMS 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 BMS 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 BMS (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 BMS in hypertensive type 2 diabetic patients is based on studies where irbesartan was used in addition to other antihypertensive agents, as needed, to reach target blood pressure (see section 5.1).

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

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

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

Paediatric patients: irbesartan is not recommended for use in children and adolescents due to insufficient data on safety and efficacy (see sections 4.8, 5.1 and 5.2).

## 4.3 Contraindications

Hypersensitivity to the active substance, or to any of the excipients (see section 6.1).
Second and third 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 BMS.

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 BMS, a similar effect should be anticipated with angiotensin-II receptor antagonists.

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

**4.5 Interaction with other medicinal products and other forms of interaction**

Diuretics and other antihypertensive agents: other antihypertensive agents may increase the hypotensive effects of irbesartan; however Irbesartan BMS 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 BMS (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 coadministration of irbesartan.

## 4.6 Pregnancy and lactation

Pregnancy:

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

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Antagonists (AIIRAs), similar risks may exist for this class of drugs. Unless continued 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 BMS during breast-feeding, Irbesartan BMS is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

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

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

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

The frequency of adverse reactions listed below is defined using the following convention:

very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

*Investigations:*

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

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

*Cardiac disorders:*

Uncommon: tachycardia

*Nervous system disorders:*

Common: dizziness, orthostatic dizziness*

*Respiratory, thoracic and mediastinal disorders:*

Uncommon: cough

*Gastrointestinal disorders:*

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

*Musculoskeletal and connective tissue disorders:*

Common: musculoskeletal pain*

*Vascular disorders:*

Common: orthostatic hypotension*
Uncommon: flushing

*General disorders and administration site conditions:*

Common: fatigue
Uncommon: chest pain

*Reproductive system and breast disorders:*

Uncommon: sexual dysfunction

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

*Nervous system disorders:*

Headache

*Ear and labyrinth disorders:*

Tinnitus

*Gastrointestinal disorders:*
Dysgeusia

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

*Skin and subcutaneous tissue disorders:*
Leukocytoclastic vasculitis

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

*Metabolism and nutrition disorders:*
Hyperkalaemia

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

*Hepato-biliary disorders:*
Hepatitis, abnormal liver function

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

### 4.9 Overdose

Experience in adults exposed to doses of up to 900 mg/day for 8 weeks revealed no toxicity. The most likely manifestations of 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 BMS. 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 $AT_1$) antagonist. It is expected to block all actions of angiotensin-II mediated by the $AT_1$ receptor, regardless of the source or route of synthesis of angiotensin-II. The selective antagonism of the angiotensin-II ($AT_1$) receptors results in increases in plasma renin levels and angiotensin-II levels, and a decrease in plasma aldosterone concentration. Serum potassium levels are not significantly affected by irbesartan alone at the recommended doses. Irbesartan does not inhibit ACE (kininase-II), an enzyme which generates angiotensin-II and also degrades bradykinin into inactive metabolites. Irbesartan does not require metabolic activation for its activity.

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 BMS 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 BMS is not influenced by age or gender. As is the case with other medicinal products that affect the renin-angiotensin system, black hypertensive patients have notably less response to irbesartan monotherapy. When irbesartan is administered concomitantly with a low dose of hydrochlorothiazide (e.g. 12.5 mg daily), the antihypertensive response in black patients approaches that of white patients.
There is no clinically important effect on serum uric acid or urinary uric acid secretion.

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

Hypertension and type 2 diabetes with renal disease
The “Irbesartan Diabetic Nephropathy Trial (IDNT)” shows that irbesartan decreases the progression of renal disease in patients with chronic renal insufficiency and overt proteinuria. IDNT was a double blind, controlled, morbidity and mortality trial comparing Irbesartan BMS, 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 BMS 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 BMS, from 2.5 mg to 10 mg amlodipine, or placebo as tolerated. Patients in all treatment groups typically received between 2 and 4 antihypertensive agents (e.g., diuretics, beta blockers, alpha blockers) to reach a predefined blood pressure goal of ≤ 135/85 mmHg or a 10 mmHg reduction in systolic pressure if baseline was > 160 mmHg. Sixty per cent (60%) of patients in the placebo group reached this target blood pressure whereas this figure was 76% and 78% in the irbesartan and amlodipine groups respectively. Irbesartan significantly reduced the relative risk in the primary combined endpoint of doubling serum creatinine, end-stage renal disease (ESRD) or all-cause mortality. Approximately 33% of patients in the irbesartan group reached the primary renal composite endpoint compared to 39% and 41% in the placebo and amlodipine groups [20% relative risk reduction versus placebo (p = 0.024) and 23% relative risk reduction compared to amlodipine (p = 0.006)]. When the individual components of the primary endpoint were

analysed, no effect in all cause mortality was observed, while a positive trend in the reduction in ESRD and a significant reduction in doubling of serum creatinine were observed.

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

The study of the "Effects of Irbesartan on Microalbuminuria in Hypertensive Patients with type 2 Diabetes Mellitus (IRMA 2)" shows that irbesartan 300 mg delays progression to overt proteinuria in patients with microalbuminuria. IRMA 2 was a placebo-controlled double blind morbidity study in 590 patients with type 2 diabetes, microalbuminuria (30-300 mg/day) and normal renal function (serum creatinine ≤ 1.5 mg/dl in males and < 1.1 mg/dl in females). The study examined the long-term effects (2 years) of Irbesartan BMS 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 BMS 300 mg group (34%) than in the placebo group (21%).



## 5.2 Pharmacokinetic properties

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

Irbesartan exhibits linear and dose proportional pharmacokinetics over the dose range of 10 to 600 mg. A less than proportional increase in oral absorption at doses beyond 600 mg (twice the maximal recommended dose) was observed; the mechanism for this is unknown. Peak plasma concentrations are attained at 1.5 - 2 hours after oral administration. The total body and renal clearance are 157 - 176 and 3 - 3.5 ml/min, respectively. The terminal elimination half-life of irbesartan is 11 - 15 hours. Steady-state plasma concentrations are attained within 3 days after initiation of a once-daily dosing regimen. Limited accumulation of irbesartan (< 20%) is observed in plasma upon repeated once-daily dosing. In a study, somewhat higher plasma concentrations of irbesartan were observed in female hypertensive patients. However, there was no difference in the half-life and accumulation of irbesartan. No dosage adjustment is necessary in female patients. Irbesartan AUC and $C_{max}$ values were also somewhat greater in elderly subjects (≥ 65 years) than those of young subjects

(18 - 40 years). However the terminal half-life was not significantly altered. No dosage adjustment is necessary in elderly patients.

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

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

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

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



### 5.3 Preclinical safety data

There was no evidence of abnormal systemic or target organ toxicity at clinically relevant doses. In non-clinical safety studies, high doses of irbesartan (≥ 250 mg/kg/day in rats and ≥ 100 mg/kg/day in macaques) caused a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit). At very high doses (≥ 500 mg/kg/day) degenerative changes in the kidney (such as interstitial nephritis, tubular distension, basophilic tubules, increased plasma concentrations of urea and creatinine) were induced by irbesartan in the rat and the macaque and are considered secondary to the hypotensive effects of the medicinal product which led to decreased renal perfusion. Furthermore, irbesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells (in rats at ≥ 90 mg/kg/day, in macaques at ≥ 10 mg/kg/day). All of these changes were considered to be caused by the pharmacological action of irbesartan. For therapeutic doses of irbesartan in humans, the hyperplasia/ hypertrophy of the renal juxtaglomerular cells does not appear to have any relevance.

There was no evidence of mutagenicity, clastogenicity or carcinogenicity.

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

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet core:
Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Hypromellose
Silicon dioxide
Magnesium stearate.

Film-coating:
Lactose monohydrate
Hypromellose
Titanium dioxide
Macrogol 3000
Carnauba wax.

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Do not store above 30°C.

### 6.5 Nature and contents of container

Cartons of 14 film-coated tablets: 1 blister card of 14 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 28 film-coated tablets: 2 blister cards of 14 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 56 film-coated tablets: 4 blister cards of 14 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 84 film-coated tablets: 6 blister cards of 14 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 98 film-coated tablets: 7 blister cards of 14 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 56 x 1 film-coated tablet; 7 blister cards of 8 x 1 film-coated tablet each in PVC/PVDC/Aluminium perforated unit dose blisters.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

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

## 7. MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH - United Kingdom

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/06/375/016-021

## 9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 January 2007
Date of latest renewal:

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

## 1. NAME OF THE MEDICINAL PRODUCT

Irbesartan BMS 150 mg film-coated tablets.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg of irbesartan.

Excipient: 51.00 mg of lactose monohydrate per film-coated tablet.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.
White to off-white, biconvex, and oval-shaped with a heart debossed on one side and the number 2872 engraved on the other side.



## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

### 4.2 Posology and method of administration

The usual recommended initial and maintenance dose is 150 mg once daily, with or without food. Irbesartan BMS 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 BMS 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 BMS (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 BMS in hypertensive type 2 diabetic patients is based on studies where irbesartan was used in addition to other antihypertensive agents, as needed, to reach target blood pressure (see section 5.1).

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

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

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

Paediatric patients: irbesartan is not recommended for use in children and adolescents due to insufficient data on safety and efficacy (see sections 4.8, 5.1 and 5.2).

## 4.3 Contraindications

Hypersensitivity to the active substance, or to any of the excipients (see section 6.1).
Second and third 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 BMS.

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 BMS, a similar effect should be anticipated with angiotensin-II receptor antagonists.

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

**4.5 Interaction with other medicinal products and other forms of interaction**

Diuretics and other antihypertensive agents: other antihypertensive agents may increase the hypotensive effects of irbesartan; however Irbesartan BMS 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 BMS (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 coadministration of irbesartan.

## 4.6 Pregnancy and lactation

Pregnancy:

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

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Antagonists (AIIRAs), similar risks may exist for this class of drugs. Unless continued 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 BMS during breast-feeding, Irbesartan BMS is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

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

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

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

The frequency of adverse reactions listed below is defined using the following convention:

very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

*Investigations:*

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

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

*Cardiac disorders:*

Uncommon: tachycardia

*Nervous system disorders:*

Common: dizziness, orthostatic dizziness*

*Respiratory, thoracic and mediastinal disorders:*

Uncommon: cough

*Gastrointestinal disorders:*

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

*Musculoskeletal and connective tissue disorders:*

Common: musculoskeletal pain*

*Vascular disorders:*

Common: orthostatic hypotension*
Uncommon: flushing

*General disorders and administration site conditions:*

Common: fatigue
Uncommon: chest pain

*Reproductive system and breast disorders:*

Uncommon: sexual dysfunction

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

*Nervous system disorders:*

Headache

*Ear and labyrinth disorders:*

Tinnitus

*Gastrointestinal disorders:*
Dysgeusia

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

*Skin and subcutaneous tissue disorders:*
Leukocytoclastic vasculitis

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

*Metabolism and nutrition disorders:*
Hyperkalaemia

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

*Hepato-biliary disorders:*
Hepatitis, abnormal liver function

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

### 4.9 Overdose

Experience in adults exposed to doses of up to 900 mg/day for 8 weeks revealed no toxicity. The most likely manifestations of 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 BMS. 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 $AT_1$) antagonist. It is expected to block all actions of angiotensin-II mediated by the $AT_1$ receptor, regardless of the source or route of synthesis of angiotensin-II. The selective antagonism of the angiotensin-II ($AT_1$) receptors results in increases in plasma renin levels and angiotensin-II levels, and a decrease in plasma aldosterone concentration. Serum potassium levels are not significantly affected by irbesartan alone at the recommended doses. Irbesartan does not inhibit ACE (kininase-II), an enzyme which generates angiotensin-II and also degrades bradykinin into inactive metabolites. Irbesartan does not require metabolic activation for its activity.

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 BMS 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 BMS is not influenced by age or gender. As is the case with other medicinal products that affect the renin-angiotensin system, black hypertensive patients have notably less response to irbesartan monotherapy. When irbesartan is administered concomitantly with a low dose of hydrochlorothiazide (e.g. 12.5 mg daily), the antihypertensive response in black patients approaches that of white patients.
There is no clinically important effect on serum uric acid or urinary uric acid secretion.

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

Hypertension and type 2 diabetes with renal disease
The “Irbesartan Diabetic Nephropathy Trial (IDNT)” shows that irbesartan decreases the progression of renal disease in patients with chronic renal insufficiency and overt proteinuria. IDNT was a double blind, controlled, morbidity and mortality trial comparing Irbesartan BMS, 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 BMS 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 BMS, from 2.5 mg to 10 mg amlodipine, or placebo as tolerated. Patients in all treatment groups typically received between 2 and 4 antihypertensive agents (e.g., diuretics, beta blockers, alpha blockers) to reach a predefined blood pressure goal of ≤ 135/85 mmHg or a 10 mmHg reduction in systolic pressure if baseline was > 160 mmHg. Sixty per cent (60%) of patients in the placebo group reached this target blood pressure whereas this figure was 76% and 78% in the irbesartan and amlodipine groups respectively. Irbesartan significantly reduced the relative risk in the primary combined endpoint of doubling serum creatinine, end-stage renal disease (ESRD) or all-cause mortality. Approximately 33% of patients in the irbesartan group reached the primary renal composite endpoint compared to 39% and 41% in the placebo and amlodipine groups [20% relative risk reduction versus placebo (p = 0.024) and 23% relative risk reduction compared to amlodipine (p = 0.006)]. When the individual components of the primary endpoint were

analysed, no effect in all cause mortality was observed, while a positive trend in the reduction in ESRD and a significant reduction in doubling of serum creatinine were observed.

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

The study of the "Effects of Irbesartan on Microalbuminuria in Hypertensive Patients with type 2 Diabetes Mellitus (IRMA 2)" shows that irbesartan 300 mg delays progression to overt proteinuria in patients with microalbuminuria. IRMA 2 was a placebo-controlled double blind morbidity study in 590 patients with type 2 diabetes, microalbuminuria (30-300 mg/day) and normal renal function (serum creatinine ≤ 1.5 mg/dl in males and < 1.1 mg/dl in females). The study examined the long-term effects (2 years) of Irbesartan BMS 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 BMS 300 mg group (34%) than in the placebo group (21%).



## 5.2 Pharmacokinetic properties

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

Irbesartan exhibits linear and dose proportional pharmacokinetics over the dose range of 10 to 600 mg. A less than proportional increase in oral absorption at doses beyond 600 mg (twice the maximal recommended dose) was observed; the mechanism for this is unknown. Peak plasma concentrations are attained at 1.5 - 2 hours after oral administration. The total body and renal clearance are 157 - 176 and 3 - 3.5 ml/min, respectively. The terminal elimination half-life of irbesartan is 11 - 15 hours. Steady-state plasma concentrations are attained within 3 days after initiation of a once-daily dosing regimen. Limited accumulation of irbesartan (< 20%) is observed in plasma upon repeated once-daily dosing. In a study, somewhat higher plasma concentrations of irbesartan were observed in female hypertensive patients. However, there was no difference in the half-life and accumulation of irbesartan. No dosage adjustment is necessary in female patients. Irbesartan AUC and $C_{max}$ values were also somewhat greater in elderly subjects (≥ 65 years) than those of young subjects

(18 - 40 years). However the terminal half-life was not significantly altered. No dosage adjustment is necessary in elderly patients.

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

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

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

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



### 5.3 Preclinical safety data

There was no evidence of abnormal systemic or target organ toxicity at clinically relevant doses. In non-clinical safety studies, high doses of irbesartan (≥ 250 mg/kg/day in rats and ≥ 100 mg/kg/day in macaques) caused a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit). At very high doses (≥ 500 mg/kg/day) degenerative changes in the kidney (such as interstitial nephritis, tubular distension, basophilic tubules, increased plasma concentrations of urea and creatinine) were induced by irbesartan in the rat and the macaque and are considered secondary to the hypotensive effects of the medicinal product which led to decreased renal perfusion. Furthermore, irbesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells (in rats at ≥ 90 mg/kg/day, in macaques at ≥ 10 mg/kg/day). All of these changes were considered to be caused by the pharmacological action of irbesartan. For therapeutic doses of irbesartan in humans, the hyperplasia/ hypertrophy of the renal juxtaglomerular cells does not appear to have any relevance.

There was no evidence of mutagenicity, clastogenicity or carcinogenicity.

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

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet core:
Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Hypromellose
Silicon dioxide
Magnesium stearate.

Film-coating:
Lactose monohydrate
Hypromellose
Titanium dioxide
Macrogol 3000
Carnauba wax.

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Do not store above 30°C.

### 6.5 Nature and contents of container

Cartons of 14 film-coated tablets: 1 blister card of 14 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 28 film-coated tablets: 2 blister cards of 14 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 56 film-coated tablets: 4 blister cards of 14 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 84 film-coated tablets: 6 blister cards of 14 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 98 film-coated tablets: 7 blister cards of 14 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 56 x 1 film-coated tablet; 7 blister cards of 8 x 1 film-coated tablet each in PVC/PVDC/Aluminium perforated unit dose blisters.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

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

## 7. MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH - United Kingdom

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/06/375/022-027

## 9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 January 2007
Date of latest renewal:

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

## 1. NAME OF THE MEDICINAL PRODUCT

Irbesartan BMS 300 mg film-coated tablets.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg of irbesartan.

Excipient: 102.00 mg of lactose monohydrate per film-coated tablet.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.
White to off-white, biconvex, and oval-shaped with a heart debossed on one side and the number 2873 engraved on the other side.



## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

### 4.2 Posology and method of administration

The usual recommended initial and maintenance dose is 150 mg once daily, with or without food. Irbesartan BMS 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 BMS 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 BMS (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 BMS in hypertensive type 2 diabetic patients is based on studies where irbesartan was used in addition to other antihypertensive agents, as needed, to reach target blood pressure (see section 5.1).

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

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

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

Paediatric patients: irbesartan is not recommended for use in children and adolescents due to insufficient data on safety and efficacy (see sections 4.8, 5.1 and 5.2).

## 4.3 Contraindications

Hypersensitivity to the active substance, or to any of the excipients (see section 6.1).
Second and third 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 BMS.

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 BMS, a similar effect should be anticipated with angiotensin-II receptor antagonists.

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

**4.5 Interaction with other medicinal products and other forms of interaction**

Diuretics and other antihypertensive agents: other antihypertensive agents may increase the hypotensive effects of irbesartan; however Irbesartan BMS 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 BMS (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 coadministration of irbesartan.

## 4.6 Pregnancy and lactation

Pregnancy:

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

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Antagonists (AIIRAs), similar risks may exist for this class of drugs. Unless continued 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 BMS during breast-feeding, Irbesartan BMS is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

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

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

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

The frequency of adverse reactions listed below is defined using the following convention:

very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

*Investigations:*

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

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

*Cardiac disorders:*

Uncommon: tachycardia

*Nervous system disorders:*

Common: dizziness, orthostatic dizziness*

*Respiratory, thoracic and mediastinal disorders:*

Uncommon: cough

*Gastrointestinal disorders:*

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

*Musculoskeletal and connective tissue disorders:*

Common: musculoskeletal pain*

*Vascular disorders:*

Common: orthostatic hypotension*
Uncommon: flushing

*General disorders and administration site conditions:*

Common: fatigue
Uncommon: chest pain

*Reproductive system and breast disorders:*

Uncommon: sexual dysfunction

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

*Nervous system disorders:*

Headache

*Ear and labyrinth disorders:*

Tinnitus

*Gastrointestinal disorders:*
Dysgeusia

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

*Skin and subcutaneous tissue disorders:*
Leukocytoclastic vasculitis

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

*Metabolism and nutrition disorders:*
Hyperkalaemia

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

*Hepato-biliary disorders:*
Hepatitis, abnormal liver function

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

### 4.9 Overdose

Experience in adults exposed to doses of up to 900 mg/day for 8 weeks revealed no toxicity. The most likely manifestations of 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 BMS. 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 $AT_1$) antagonist. It is expected to block all actions of angiotensin-II mediated by the $AT_1$ receptor, regardless of the source or route of synthesis of angiotensin-II. The selective antagonism of the angiotensin-II ($AT_1$) receptors results in increases in plasma renin levels and angiotensin-II levels, and a decrease in plasma aldosterone concentration. Serum potassium levels are not significantly affected by irbesartan alone at the recommended doses. Irbesartan does not inhibit ACE (kininase-II), an enzyme which generates angiotensin-II and also degrades bradykinin into inactive metabolites. Irbesartan does not require metabolic activation for its activity.

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 BMS 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 BMS is not influenced by age or gender. As is the case with other medicinal products that affect the renin-angiotensin system, black hypertensive patients have notably less response to irbesartan monotherapy. When irbesartan is administered concomitantly with a low dose of hydrochlorothiazide (e.g. 12.5 mg daily), the antihypertensive response in black patients approaches that of white patients.
There is no clinically important effect on serum uric acid or urinary uric acid secretion.

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

Hypertension and type 2 diabetes with renal disease
The “Irbesartan Diabetic Nephropathy Trial (IDNT)” shows that irbesartan decreases the progression of renal disease in patients with chronic renal insufficiency and overt proteinuria. IDNT was a double blind, controlled, morbidity and mortality trial comparing Irbesartan BMS, 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 BMS 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 BMS, from 2.5 mg to 10 mg amlodipine, or placebo as tolerated. Patients in all treatment groups typically received between 2 and 4 antihypertensive agents (e.g., diuretics, beta blockers, alpha blockers) to reach a predefined blood pressure goal of ≤ 135/85 mmHg or a 10 mmHg reduction in systolic pressure if baseline was > 160 mmHg. Sixty per cent (60%) of patients in the placebo group reached this target blood pressure whereas this figure was 76% and 78% in the irbesartan and amlodipine groups respectively. Irbesartan significantly reduced the relative risk in the primary combined endpoint of doubling serum creatinine, end-stage renal disease (ESRD) or all-cause mortality. Approximately 33% of patients in the irbesartan group reached the primary renal composite endpoint compared to 39% and 41% in the placebo and amlodipine groups [20% relative risk reduction versus placebo (p = 0.024) and 23% relative risk reduction compared to amlodipine (p = 0.006)]. When the individual components of the primary endpoint were

analysed, no effect in all cause mortality was observed, while a positive trend in the reduction in ESRD and a significant reduction in doubling of serum creatinine were observed.

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

The study of the "Effects of Irbesartan on Microalbuminuria in Hypertensive Patients with type 2 Diabetes Mellitus (IRMA 2)" shows that irbesartan 300 mg delays progression to overt proteinuria in patients with microalbuminuria. IRMA 2 was a placebo-controlled double blind morbidity study in 590 patients with type 2 diabetes, microalbuminuria (30-300 mg/day) and normal renal function (serum creatinine ≤ 1.5 mg/dl in males and < 1.1 mg/dl in females). The study examined the long-term effects (2 years) of Irbesartan BMS 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 BMS 300 mg group (34%) than in the placebo group (21%).



## 5.2 Pharmacokinetic properties

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

Irbesartan exhibits linear and dose proportional pharmacokinetics over the dose range of 10 to 600 mg. A less than proportional increase in oral absorption at doses beyond 600 mg (twice the maximal recommended dose) was observed; the mechanism for this is unknown. Peak plasma concentrations are attained at 1.5 - 2 hours after oral administration. The total body and renal clearance are 157 - 176 and 3 - 3.5 ml/min, respectively. The terminal elimination half-life of irbesartan is 11 - 15 hours. Steady-state plasma concentrations are attained within 3 days after initiation of a once-daily dosing regimen. Limited accumulation of irbesartan (< 20%) is observed in plasma upon repeated once-daily dosing. In a study, somewhat higher plasma concentrations of irbesartan were observed in female hypertensive patients. However, there was no difference in the half-life and accumulation of irbesartan. No dosage adjustment is necessary in female patients. Irbesartan AUC and $C_{max}$ values were also somewhat greater in elderly subjects (≥ 65 years) than those of young subjects

(18 - 40 years). However the terminal half-life was not significantly altered. No dosage adjustment is necessary in elderly patients.

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

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

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

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



### 5.3 Preclinical safety data

There was no evidence of abnormal systemic or target organ toxicity at clinically relevant doses. In non-clinical safety studies, high doses of irbesartan (≥ 250 mg/kg/day in rats and ≥ 100 mg/kg/day in macaques) caused a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit). At very high doses (≥ 500 mg/kg/day) degenerative changes in the kidney (such as interstitial nephritis, tubular distension, basophilic tubules, increased plasma concentrations of urea and creatinine) were induced by irbesartan in the rat and the macaque and are considered secondary to the hypotensive effects of the medicinal product which led to decreased renal perfusion. Furthermore, irbesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells (in rats at ≥ 90 mg/kg/day, in macaques at ≥ 10 mg/kg/day). All of these changes were considered to be caused by the pharmacological action of irbesartan. For therapeutic doses of irbesartan in humans, the hyperplasia/ hypertrophy of the renal juxtaglomerular cells does not appear to have any relevance.

There was no evidence of mutagenicity, clastogenicity or carcinogenicity.

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

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet core:
Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Hypromellose
Silicon dioxide
Magnesium stearate.

Film-coating:
Lactose monohydrate
Hypromellose
Titanium dioxide
Macrogol 3000
Carnauba wax.

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Do not store above 30°C.

### 6.5 Nature and contents of container

Cartons of 14 film-coated tablets: 1 blister card of 14 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 28 film-coated tablets: 2 blister cards of 14 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 56 film-coated tablets: 4 blister cards of 14 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 84 film-coated tablets: 6 blister cards of 14 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 98 film-coated tablets: 7 blister cards of 14 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 56 x 1 film-coated tablet; 7 blister cards of 8 x 1 film-coated tablet each in PVC/PVDC/Aluminium perforated unit dose blisters.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

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

## 7. MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH - United Kingdom

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/06/375/028-033

## 9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 January 2007
Date of latest renewal:

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

**ANNEX II**

**A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OF THE MARKETING AUTHORISATION**

## A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Sanofi Winthrop Industrie
1 rue de la Vierge
Ambarès & Lagrave
F-33565 Carbon Blanc Cedex
France

Sanofi-Synthelabo Limited
Edgefield Avenue,
Fawdon
Newcastle Upon Tyne,
Tyne & Wear NE3 3TT
United Kingdom

Sanofi Winthrop Industrie
30-36 Avenue Gustave Eiffel, BP 7166
F-37071 Tours Cedex 2
France

Chinoin Private Co. Ltd.
Lévai u.5.
2112 Veresegyhaz
Hungary

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

The PSUR cycle of Irbesartan BMS is aligned with the cross-referred product, KARVEA, until otherwise specified.

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in version 3.0 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

**A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Irbesartan BMS 75 mg tablets
irbesartan

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains: irbesartan 75 mg

## 3. LIST OF EXCIPIENTS

Excipients: also contains lactose monohydrate.

## 4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets
28 tablets
56 tablets
56 x 1 tablets
98 tablets

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

Oral use. Read the package leaflet before use.

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

Keep out of the reach and sight of children.



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

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

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

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

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH - United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/375/001 - 14 tablets
EU/1/06/375/002 - 28 tablets
EU/1/06/375/003 - 56 tablets
EU/1/06/375/004 - 56 x 1 tablets
EU/1/06/375/005 - 98 tablets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Irbesartan BMS 75 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**1. NAME OF THE MEDICINAL PRODUCT**

Irbesartan BMS 75 mg tablets
irbesartan

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

BRISTOL-MYERS SQUIBB PHARMA EEIG

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

14 - 28 - 56 - 98 tablets:
Mon
Tue
Wed
Thu
Fri
Sat
Sun

56 x 1 tablets:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Irbesartan BMS 150 mg tablets
irbesartan

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains: irbesartan 150 mg

## 3. LIST OF EXCIPIENTS

Excipients: also contains lactose monohydrate.

## 4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets
28 tablets
56 tablets
56 x 1 tablets
98 tablets

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

Oral use. Read the package leaflet before use.

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

Keep out of the reach and sight of children.



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

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

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

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

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH - United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/375/006 - 14 tablets
EU/1/06/375/007 - 28 tablets
EU/1/06/375/008 - 56 tablets
EU/1/06/375/009 - 56 x 1 tablets
EU/1/06/375/010 - 98 tablets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Irbesartan BMS 150 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**1. NAME OF THE MEDICINAL PRODUCT**

Irbesartan BMS 150 mg tablets
irbesartan

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

BRISTOL-MYERS SQUIBB PHARMA EEIG

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

14 - 28 - 56 - 98 tablets:
Mon
Tue
Wed
Thu
Fri
Sat
Sun

56 x 1 tablets:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Irbesartan BMS 300 mg tablets
irbesartan

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains: irbesartan 300 mg

## 3. LIST OF EXCIPIENTS

Excipients: also contains lactose monohydrate.

## 4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets
28 tablets
56 tablets
56 x 1 tablets
98 tablets

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

Oral use. Read the package leaflet before use.

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

Keep out of the reach and sight of children.



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

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

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

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

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH - United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/375/011 - 14 tablets
EU/1/06/375/012 - 28 tablets
EU/1/06/375/013 - 56 tablets
EU/1/06/375/014 - 56 x 1 tablets
EU/1/06/375/015 - 98 tablets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Irbesartan BMS 300 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**1. NAME OF THE MEDICINAL PRODUCT**

Irbesartan BMS 300 mg tablets
irbesartan

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

BRISTOL-MYERS SQUIBB PHARMA EEIG

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

14 - 28 - 56 - 98 tablets:
Mon
Tue
Wed
Thu
Fri
Sat
Sun

56 x 1 tablets:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Irbesartan BMS 75 mg film-coated tablets
irbesartan

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains: irbesartan 75 mg

## 3. LIST OF EXCIPIENTS

Excipients: also contains lactose monohydrate.

## 4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets
28 tablets
56 tablets
56 x 1 tablets
84 tablets
98 tablets

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

Oral use. Read the package leaflet before use.

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

Keep out of the reach and sight of children.



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

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

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

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

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH - United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/375/016 - 14 tablets
EU/1/06/375/017 - 28 tablets
EU/1/06/375/018 - 56 tablets
EU/1/06/375/019 - 56 x 1 tablets
EU/1/06/375/020 - 84 tablets
EU/1/06/375/021 - 98 tablets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Irbesartan BMS 75 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**1. NAME OF THE MEDICINAL PRODUCT**

Irbesartan BMS 75 mg tablets
irbesartan

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

BRISTOL-MYERS SQUIBB PHARMA EEIG

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

14 - 28 - 56 - 84 - 98 tablets:
Mon
Tue
Wed
Thu
Fri
Sat
Sun

56 x 1 tablets:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Irbesartan BMS 150 mg film-coated tablets
irbesartan

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains: irbesartan 150 mg

## 3. LIST OF EXCIPIENTS

Excipients: also contains lactose monohydrate.

## 4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets
28 tablets
56 tablets
56 x 1 tablets
84 tablets
98 tablets

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

Oral use. Read the package leaflet before use.

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

Keep out of the reach and sight of children.



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

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

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

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

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH - United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/375/022 - 14 tablets
EU/1/06/375/023 - 28 tablets
EU/1/06/375/024 - 56 tablets
EU/1/06/375/025 - 56 x 1 tablets
EU/1/06/375/026 - 84 tablets
EU/1/06/375/027 - 98 tablets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Irbesartan BMS 150 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**1. NAME OF THE MEDICINAL PRODUCT**

Irbesartan BMS 150 mg tablets
irbesartan

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

BRISTOL-MYERS SQUIBB PHARMA EEIG

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

14 - 28 - 56 - 84 - 98 tablets:
Mon
Tue
Wed
Thu
Fri
Sat
Sun

56 x 1 tablets:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Irbesartan BMS 300 mg film-coated tablets
irbesartan

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains: irbesartan 300 mg

## 3. LIST OF EXCIPIENTS

Excipients: also contains lactose monohydrate.

## 4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets
28 tablets
56 tablets
56 x 1 tablets
84 tablets
98 tablets

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

Oral use. Read the package leaflet before use.

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

Keep out of the reach and sight of children.



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

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

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

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

BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH - United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/375/028 - 14 tablets
EU/1/06/375/029 - 28 tablets
EU/1/06/375/030 - 56 tablets
EU/1/06/375/031 - 56 x 1 tablets
EU/1/06/375/032 - 84 tablets
EU/1/06/375/033 - 98 tablets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Irbesartan BMS 300 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**1. NAME OF THE MEDICINAL PRODUCT**

Irbesartan BMS 300 mg tablets
irbesartan

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

BRISTOL-MYERS SQUIBB PHARMA EEIG

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

14 - 28 - 56 - 84 - 98 tablets:
Mon
Tue
Wed
Thu
Fri
Sat
Sun

56 x 1 tablets:

**B. PACKAGE LEAFLET**

**PACKAGE LEAFLET: INFORMATION FOR THE USER**
**Irbesartan BMS 75 mg tablets**
irbesartan

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

**In this leaflet:**




## 1. WHAT IRBESARTAN BMS IS AND WHAT IT IS USED FOR

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

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

## 2. BEFORE YOU TAKE IRBESARTAN BMS

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

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

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

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

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

Irbesartan BMS does not usually interact with other medicines.

**You may need to have blood checks if you take:**
- potassium supplements
- salt substitutes containing potassium
- potassium-sparing medicines (such as certain diuretics)
- medicines containing lithium

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

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

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

**Breast-feeding**
Tell your doctor if you are breast-feeding or about to start breast-feeding. Irbesartan BMS is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

**Driving and using machines**
No studies on the effects on the ability to drive and use machines have been performed. Irbesartan BMS is unlikely to affect your ability to drive or use machines. However, occasionally dizziness or weariness may occur during treatment of high blood pressure. If you experience these, talk to your doctor before attempting to drive or use machines.

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



## 3. HOW TO TAKE IRBESARTAN BMS

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

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

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

- **Patients with high blood pressure and type 2 diabetes with kidney disease**
  In patients with high blood pressure and type 2 diabetes, 300 mg (four tablets a day) once daily is the preferred maintenance dose for the treatment of associated kidney disease.

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

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

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

**Children should not take Irbesartan BMS**
Irbesartan BMS should not be given to children under 18 years of age. If a child swallows some tablets, contact your doctor immediately.

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

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

## 4. POSSIBLE SIDE EFFECTS

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

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

The frequency of the side effects listed below is defined using the following convention:
Very common: at least 1 in 10 patients or more
Common: at least 1 in 100 and less than 1 in 10 patients
Uncommon: at least 1 in 1000 and less than 1 in 100 patients

Side effects reported in clinical studies for patients treated with Irbesartan BMS were:
- Very common: if you suffer from high blood pressure and type 2 diabetes with kidney disease, blood tests may show an increased level of potassium.

- Common: dizziness, feeling sick/vomiting, fatigue and blood tests may show raised levels of an enzyme that measures the muscle and heart function (creatine kinase enzyme). In patients with high blood pressure and type 2 diabetes with kidney disease, dizziness when getting up from a lying or sitting position, low blood pressure when getting up from a lying or sitting position, pain in joints or muscles and decreased levels of a protein in the red blood cells (haemoglobin) were also reported.

- Uncommon: heart rate increased, flushing, cough, diarrhoea, indigestion/heartburn, sexual dysfunction (problems with sexual performance), chest pain.

Some undesirable effects have been reported since marketing of Irbesartan BMS but the frequency for them to occur is not known. These undesirable effects are: headache, taste disturbance, ringing in the ears, muscle cramps, pain in joints and muscles, abnormal liver function, increased blood potassium

levels, impaired kidney function, and inflammation of small blood vessels mainly affecting the skin (a condition known as leukocytoclastic vasculitis).

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

## 5. HOW TO STORE IRBESARTAN BMS

Keep out of the reach and sight of children.

Do not use Irbesartan BMS 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 30°C.

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 BMS contains**

- The active substance is irbesartan. Each tablet of Irbesartan BMS 75 mg contains 75 mg irbesartan.
- The other ingredients are microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, magnesium stearate, colloidal hydrated silica, pregelatinised maize starch, and poloxamer 188.

**What Irbesartan BMS looks like and contents of the pack**

Irbesartan BMS 75 mg tablets are white to off-white, biconvex, and oval-shaped with a heart debossed on one side and the number 2771 engraved on the other side.

Irbesartan BMS 75 mg tablets are supplied in blister packs of 14, 28, 56 or 98 tablets. Unidose blister packs of 56 x 1 tablet for delivery in hospitals are also available.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder:**
BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH - United Kingdom

**Manufacturer:**
SANOFI WINTHROP INDUSTRIE
1, rue de la Vierge
Ambarès & Lagrave
F-33565 Carbon Blanc Cedex - France

SANOFI SYNTHELABO LIMITED
Edgefield Avenue - Fawdon
Newcastle Upon Tyne, Tyne & Wear NE3 3TT - United Kingdom

SANOFI WINTHROP INDUSTRIE
30-36 Avenue Gustave Eiffel, BP 7166
F-37071 Tours Cedex 2 - France

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

**Belgique/België/Belgien**
BRISTOL-MYERS SQUIBB BELGIUM S.A./N.V.
Tél/Tel: + 32 2 352 74 60

**България**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Тел.: + 359 800 12 400

**Česká republika**
BRISTOL-MYERS SQUIBB SPOL. S R.O.
Tel: + 420 221 016 111

**Danmark**
BRISTOL-MYERS SQUIBB
Tlf: + 45 45 93 05 06

**Deutschland**
BRISTOL-MYERS SQUIBB GMBH & CO. KGAA
Tel: + 49 89 121 42-0

**Eesti**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 372 640 1301

**Ελλάδα**
BRISTOL-MYERS SQUIBB A.E.
Τηλ: + 30 210 6074300

**España**
BRISTOL-MYERS SQUIBB, S.A.
Tel: + 34 91 456 53 00

**France**
BRISTOL-MYERS SQUIBB SARL
Tél: + 33 (0)810 410 500

**Ireland**
BRISTOL-MYERS SQUIBB PHARMACEUTICALS LTD
Tel: + 353 (1 800) 749 749

**Ísland**
VISTOR HF
Sími: + 354 535 7000

**Italia**
BRISTOL-MYERS SQUIBB S.R.L.
Tel: + 39 06 50 39 61

**Luxembourg/Luxemburg**
BRISTOL-MYERS SQUIBB BELGIUM S.A./N.V.
Tél/Tel: + 32 2 352 74 60

**Magyarország**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel.: + 36 1 301 9700

**Malta**
BRISTOL-MYERS SQUIBB S.R.L.
Tel: + 39 06 50 39 61

**Nederland**
BRISTOL-MYERS SQUIBB BV
Tel: + 31 34 857 42 22

**Norge**
BRISTOL-MYERS SQUIBB NORWAY LTD
Tlf: + 47 67 55 53 50

**Österreich**
BRISTOL-MYERS SQUIBB GESMBH
Tel: + 43 1 60 14 30

**Polska**
BRISTOL-MYERS SQUIBB POLSKA SP. Z O.O.
Tel.: + 48 22 5796666

**Portugal**
BRISTOL-MYERS SQUIBB FARMACÊUTICA
PORTUGUESA, S.A.
Tel: + 351 21 440 70 00

**România**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 40 (0)21 272 16 00

**Slovenija**
BRISTOL-MYERS SQUIBB SPOL. S R.O.
Tel: + 386 1 236 47 00

**Slovenská republika**
BRISTOL-MYERS SQUIBB SPOL. S R.O.
Tel: + 421 2 59298411

**Suomi/Finland**
OY BRISTOL-MYERS SQUIBB (FINLAND) AB
Puh/Tel: + 358 9 251 21 230

**Κύπρος**
ΑΚΗΣ ΠΑΝΑΓΙΩΤΟΥ & ΥΙΟΣ Ε.Π.Ε.
Τηλ: + 357 22 677038

**Latvija**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 371 67 50 21 85

**Lietuva**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 370 5 2790 762

**Sverige**
BRISTOL-MYERS SQUIBB AB
Tel: + 46 8 704 71 00

**United Kingdom**
BRISTOL-MYERS SQUIBB PHARMACEUTICALS LTD
Tel: + 44 (0800) 731 1736

**This leaflet was last approved in**

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

**PACKAGE LEAFLET: INFORMATION FOR THE USER**
**Irbesartan BMS 150 mg tablets**
irbesartan

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

**In this leaflet:**




## 1. WHAT IRBESARTAN BMS IS AND WHAT IT IS USED FOR

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

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

## 2. BEFORE YOU TAKE IRBESARTAN BMS

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

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

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

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

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

Irbesartan BMS does not usually interact with other medicines.

**You may need to have blood checks if you take:**
- potassium supplements
- salt substitutes containing potassium
- potassium-sparing medicines (such as certain diuretics)
- medicines containing lithium

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

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

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

**Breast-feeding**
Tell your doctor if you are breast-feeding or about to start breast-feeding. Irbesartan BMS is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

**Driving and using machines**
No studies on the effects on the ability to drive and use machines have been performed. Irbesartan BMS is unlikely to affect your ability to drive or use machines. However, occasionally dizziness or weariness may occur during treatment of high blood pressure. If you experience these, talk to your doctor before attempting to drive or use machines.

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



## 3. HOW TO TAKE IRBESARTAN BMS

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

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

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

- **Patients with high blood pressure and type 2 diabetes with kidney disease**
  In patients with high blood pressure and type 2 diabetes, 300 mg (two tablets a day) once daily is the preferred maintenance dose for the treatment of associated kidney disease.

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

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

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

**Children should not take Irbesartan BMS**
Irbesartan BMS should not be given to children under 18 years of age. If a child swallows some tablets, contact your doctor immediately.

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

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

## 4. POSSIBLE SIDE EFFECTS

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

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

The frequency of the side effects listed below is defined using the following convention:
Very common: at least 1 in 10 patients or more
Common: at least 1 in 100 and less than 1 in 10 patients
Uncommon: at least 1 in 1000 and less than 1 in 100 patients

Side effects reported in clinical studies for patients treated with Irbesartan BMS were:
- Very common: if you suffer from high blood pressure and type 2 diabetes with kidney disease, blood tests may show an increased level of potassium.

- Common: dizziness, feeling sick/vomiting, fatigue and blood tests may show raised levels of an enzyme that measures the muscle and heart function (creatine kinase enzyme). In patients with high blood pressure and type 2 diabetes with kidney disease, dizziness when getting up from a lying or sitting position, low blood pressure when getting up from a lying or sitting position, pain in joints or muscles and decreased levels of a protein in the red blood cells (haemoglobin) were also reported.

- Uncommon: heart rate increased, flushing, cough, diarrhoea, indigestion/heartburn, sexual dysfunction (problems with sexual performance), chest pain.

Some undesirable effects have been reported since marketing of Irbesartan BMS but the frequency for them to occur is not known. These undesirable effects are: headache, taste disturbance, ringing in the ears, muscle cramps, pain in joints and muscles, abnormal liver function, increased blood potassium

levels, impaired kidney function, and inflammation of small blood vessels mainly affecting the skin (a condition known as leukocytoclastic vasculitis).

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

## 5. HOW TO STORE IRBESARTAN BMS

Keep out of the reach and sight of children.

Do not use Irbesartan BMS 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 30°C.

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 BMS contains**

- The active substance is irbesartan. Each tablet of Irbesartan BMS 150 mg contains 150 mg irbesartan.
- The other ingredients are microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, magnesium stearate, colloidal hydrated silica, pregelatinised maize starch, and poloxamer 188.

**What Irbesartan BMS looks like and contents of the pack**
Irbesartan BMS 150 mg tablets are white to off-white, biconvex, and oval-shaped with a heart debossed on one side and the number 2772 engraved on the other side.

Irbesartan BMS 150 mg tablets are supplied in blister packs of 14, 28, 56 or 98 tablets. Unidose blister packs of 56 x 1 tablet for delivery in hospitals are also available.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder:**
BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH - United Kingdom

**Manufacturer:**
SANOFI WINTHROP INDUSTRIE
1, rue de la Vierge
Ambarès & Lagrave
F-33565 Carbon Blanc Cedex - France

SANOFI SYNTHELABO LIMITED
Edgefield Avenue - Fawdon
Newcastle Upon Tyne, Tyne & Wear NE3 3TT - United Kingdom

SANOFI WINTHROP INDUSTRIE
30-36 Avenue Gustave Eiffel, BP 7166
F-37071 Tours Cedex 2 - France

CHINOIN PRIVATE CO. LTD.
Lévai u.5.
2112 Veresegyház - Hungary

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

**Belgique/België/Belgien**
BRISTOL-MYERS SQUIBB BELGIUM S.A./N.V.
Tél/Tel: + 32 2 352 74 60

**България**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Тел.: + 359 800 12 400

**Česká republika**
BRISTOL-MYERS SQUIBB SPOL. S R.O.
Tel: + 420 221 016 111

**Danmark**
BRISTOL-MYERS SQUIBB
Tlf: + 45 45 93 05 06

**Deutschland**
BRISTOL-MYERS SQUIBB GMBH & CO. KGAA
Tel: + 49 89 121 42-0

**Eesti**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 372 640 1301

**Ελλάδα**
BRISTOL-MYERS SQUIBB A.E.
Τηλ: + 30 210 6074300

**España**
BRISTOL-MYERS SQUIBB, S.A.
Tel: + 34 91 456 53 00

**France**
BRISTOL-MYERS SQUIBB SARL
Tél: + 33 (0)810 410 500

**Ireland**
BRISTOL-MYERS SQUIBB PHARMACEUTICALS LTD
Tel: + 353 (1 800) 749 749

**Ísland**
VISTOR HF
Sími: + 354 535 7000

**Italia**
BRISTOL-MYERS SQUIBB S.R.L.
Tel: + 39 06 50 39 61

**Luxembourg/Luxemburg**
BRISTOL-MYERS SQUIBB BELGIUM S.A./N.V.
Tél/Tel: + 32 2 352 74 60

**Magyarország**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel.: + 36 1 301 9700

**Malta**
BRISTOL-MYERS SQUIBB S.R.L.
Tel: + 39 06 50 39 61

**Nederland**
BRISTOL-MYERS SQUIBB BV
Tel: + 31 34 857 42 22

**Norge**
BRISTOL-MYERS SQUIBB NORWAY LTD
Tlf: + 47 67 55 53 50

**Österreich**
BRISTOL-MYERS SQUIBB GESMBH
Tel: + 43 1 60 14 30

**Polska**
BRISTOL-MYERS SQUIBB POLSKA SP. Z O.O.
Tel.: + 48 22 5796666

**Portugal**
BRISTOL-MYERS SQUIBB FARMACÊUTICA
PORTUGUESA, S.A.
Tel: + 351 21 440 70 00

**România**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 40 (0)21 272 16 00

**Slovenija**
BRISTOL-MYERS SQUIBB SPOL. S R.O.
Tel: + 386 1 236 47 00

**Slovenská republika**
BRISTOL-MYERS SQUIBB SPOL. S R.O.
Tel: + 421 2 59298411

**Suomi/Finland**
OY BRISTOL-MYERS SQUIBB (FINLAND) AB
Puh/Tel: + 358 9 251 21 230

**Κύπρος**
ΑΚΗΣ ΠΑΝΑΓΙΩΤΟΥ & ΥΙΟΣ Ε.Π.Ε.
Τηλ: + 357 22 677038

**Latvija**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 371 67 50 21 85

**Lietuva**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 370 5 2790 762

**Sverige**
BRISTOL-MYERS SQUIBB AB
Tel: + 46 8 704 71 00

**United Kingdom**
BRISTOL-MYERS SQUIBB PHARMACEUTICALS LTD
Tel: + 44 (0800) 731 1736

**This leaflet was last approved in**

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

**PACKAGE LEAFLET: INFORMATION FOR THE USER**
**Irbesartan BMS 300 mg tablets**
irbesartan

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

**In this leaflet:**




## 1. WHAT IRBESARTAN BMS IS AND WHAT IT IS USED FOR

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

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

## 2. BEFORE YOU TAKE IRBESARTAN BMS

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

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

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

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

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

Irbesartan BMS does not usually interact with other medicines.

**You may need to have blood checks if you take:**
- potassium supplements
- salt substitutes containing potassium
- potassium-sparing medicines (such as certain diuretics)
- medicines containing lithium

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

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

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

**Breast-feeding**
Tell your doctor if you are breast-feeding or about to start breast-feeding. Irbesartan BMS is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

**Driving and using machines**
No studies on the effects on the ability to drive and use machines have been performed. Irbesartan BMS is unlikely to affect your ability to drive or use machines. However, occasionally dizziness or weariness may occur during treatment of high blood pressure. If you experience these, talk to your doctor before attempting to drive or use machines.

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



## 3. HOW TO TAKE IRBESARTAN BMS

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

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

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

- **Patients with high blood pressure and type 2 diabetes with kidney disease**
  In patients with high blood pressure and type 2 diabetes, 300 mg once daily is the preferred maintenance dose for the treatment of associated kidney disease.

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

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

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

**Children should not take Irbesartan BMS**
Irbesartan BMS should not be given to children under 18 years of age. If a child swallows some tablets, contact your doctor immediately.

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

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

## 4. POSSIBLE SIDE EFFECTS

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

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

The frequency of the side effects listed below is defined using the following convention:
Very common: at least 1 in 10 patients or more
Common: at least 1 in 100 and less than 1 in 10 patients
Uncommon: at least 1 in 1000 and less than 1 in 100 patients

Side effects reported in clinical studies for patients treated with Irbesartan BMS were:
- Very common: if you suffer from high blood pressure and type 2 diabetes with kidney disease, blood tests may show an increased level of potassium.

- Common: dizziness, feeling sick/vomiting, fatigue and blood tests may show raised levels of an enzyme that measures the muscle and heart function (creatine kinase enzyme). In patients with high blood pressure and type 2 diabetes with kidney disease, dizziness when getting up from a lying or sitting position, low blood pressure when getting up from a lying or sitting position, pain in joints or muscles and decreased levels of a protein in the red blood cells (haemoglobin) were also reported.

- Uncommon: heart rate increased, flushing, cough, diarrhoea, indigestion/heartburn, sexual dysfunction (problems with sexual performance), chest pain.

Some undesirable effects have been reported since marketing of Irbesartan BMS but the frequency for them to occur is not known. These undesirable effects are: headache, taste disturbance, ringing in the ears, muscle cramps, pain in joints and muscles, abnormal liver function, increased blood potassium

levels, impaired kidney function, and inflammation of small blood vessels mainly affecting the skin (a condition known as leukocytoclastic vasculitis).

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

## 5. HOW TO STORE IRBESARTAN BMS

Keep out of the reach and sight of children.

Do not use Irbesartan BMS 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 30°C.

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 BMS contains**

- The active substance is irbesartan. Each tablet of Irbesartan BMS 300 mg contains 300 mg irbesartan.
- The other ingredients are microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, magnesium stearate, colloidal hydrated silica, pregelatinised maize starch, and poloxamer 188.

**What Irbesartan BMS looks like and contents of the pack**
Irbesartan BMS 300 mg tablets are white to off-white, biconvex, and oval-shaped with a heart debossed on one side and the number 2773 engraved on the other side.

Irbesartan BMS 300 mg tablets are supplied in blister packs of 14, 28, 56 or 98 tablets. Unidose blister packs of 56 x 1 tablet for delivery in hospitals are also available.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder:**
BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH - United Kingdom

**Manufacturer:**
SANOFI WINTHROP INDUSTRIE
1, rue de la Vierge
Ambarès & Lagrave
F-33565 Carbon Blanc Cedex - France

SANOFI SYNTHELABO LIMITED
Edgefield Avenue - Fawdon
Newcastle Upon Tyne, Tyne & Wear NE3 3TT - United Kingdom

SANOFI WINTHROP INDUSTRIE
30-36 Avenue Gustave Eiffel, BP 7166
F-37071 Tours Cedex 2 - France

CHINOIN PRIVATE CO. LTD.
Lévai u.5.
2112 Veresegyház - Hungary

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

**Belgique/België/Belgien**
BRISTOL-MYERS SQUIBB BELGIUM S.A./N.V.
Tél/Tel: + 32 2 352 74 60

**Luxembourg/Luxemburg**
BRISTOL-MYERS SQUIBB BELGIUM S.A./N.V.
Tél/Tel: + 32 2 352 74 60

**България**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Тел.: + 359 800 12 400

**Magyarország**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel.: + 36 1 301 9700

**Česká republika**
BRISTOL-MYERS SQUIBB SPOL. S R.O.
Tel: + 420 221 016 111

**Malta**
BRISTOL-MYERS SQUIBB S.R.L.
Tel: + 39 06 50 39 61

**Danmark**
BRISTOL-MYERS SQUIBB
Tlf: + 45 45 93 05 06

**Nederland**
BRISTOL-MYERS SQUIBB BV
Tel: + 31 34 857 42 22

**Deutschland**
BRISTOL-MYERS SQUIBB GMBH & CO. KGAA
Tel: + 49 89 121 42-0

**Norge**
BRISTOL-MYERS SQUIBB NORWAY LTD
Tlf: + 47 67 55 53 50

**Eesti**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 372 640 1301

**Österreich**
BRISTOL-MYERS SQUIBB GESMBH
Tel: + 43 1 60 14 30

**Ελλάδα**
BRISTOL-MYERS SQUIBB A.E.
Τηλ: + 30 210 6074300

**Polska**
BRISTOL-MYERS SQUIBB POLSKA SP. Z O.O.
Tel.: + 48 22 5796666

**España**
BRISTOL-MYERS SQUIBB, S.A.
Tel: + 34 91 456 53 00

**Portugal**
BRISTOL-MYERS SQUIBB FARMACÊUTICA
PORTUGUESA, S.A.
Tel: + 351 21 440 70 00

**France**
BRISTOL-MYERS SQUIBB SARL
Tél: + 33 (0)810 410 500

**România**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 40 (0)21 272 16 00

**Ireland**
BRISTOL-MYERS SQUIBB PHARMACEUTICALS LTD
Tel: + 353 (1 800) 749 749

**Slovenija**
BRISTOL-MYERS SQUIBB SPOL. S R.O.
Tel: + 386 1 236 47 00

**Ísland**
VISTOR HF
Sími: + 354 535 7000

**Slovenská republika**
BRISTOL-MYERS SQUIBB SPOL. S R.O.
Tel: + 421 2 59298411

**Italia**
BRISTOL-MYERS SQUIBB S.R.L.
Tel: + 39 06 50 39 61

**Suomi/Finland**
OY BRISTOL-MYERS SQUIBB (FINLAND) AB
Puh/Tel: + 358 9 251 21 230

**Κύπρος**
ΑΚΗΣ ΠΑΝΑΓΙΩΤΟΥ & ΥΙΟΣ Ε.Π.Ε.
Τηλ: + 357 22 677038

**Latvija**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 371 67 50 21 85

**Lietuva**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 370 5 2790 762

**Sverige**
BRISTOL-MYERS SQUIBB AB
Tel: + 46 8 704 71 00

**United Kingdom**
BRISTOL-MYERS SQUIBB PHARMACEUTICALS LTD
Tel: + 44 (0800) 731 1736

**This leaflet was last approved in**

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

**PACKAGE LEAFLET: INFORMATION FOR THE USER**
**Irbesartan BMS 75 mg film-coated tablets**
irbesartan

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

**In this leaflet:**




## 1. WHAT IRBESARTAN BMS IS AND WHAT IT IS USED FOR

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

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

## 2. BEFORE YOU TAKE IRBESARTAN BMS

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

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

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

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

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

Irbesartan BMS does not usually interact with other medicines.

**You may need to have blood checks if you take:**
- potassium supplements
- salt substitutes containing potassium
- potassium-sparing medicines (such as certain diuretics)
- medicines containing lithium

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

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

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

**Breast-feeding**
Tell your doctor if you are breast-feeding or about to start breast-feeding. Irbesartan BMS is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

**Driving and using machines**
No studies on the effects on the ability to drive and use machines have been performed. Irbesartan BMS is unlikely to affect your ability to drive or use machines. However, occasionally dizziness or weariness may occur during treatment of high blood pressure. If you experience these, talk to your doctor before attempting to drive or use machines.

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



## 3. HOW TO TAKE IRBESARTAN BMS

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

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

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

- **Patients with high blood pressure and type 2 diabetes with kidney disease**
  In patients with high blood pressure and type 2 diabetes, 300 mg (four tablets a day) once daily is the preferred maintenance dose for the treatment of associated kidney disease.

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

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

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

**Children should not take Irbesartan BMS**
Irbesartan BMS should not be given to children under 18 years of age. If a child swallows some tablets, contact your doctor immediately.

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

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

## 4. POSSIBLE SIDE EFFECTS

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

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

The frequency of the side effects listed below is defined using the following convention:
Very common: at least 1 in 10 patients or more
Common: at least 1 in 100 and less than 1 in 10 patients
Uncommon: at least 1 in 1000 and less than 1 in 100 patients

Side effects reported in clinical studies for patients treated with Irbesartan BMS were:
- Very common: if you suffer from high blood pressure and type 2 diabetes with kidney disease, blood tests may show an increased level of potassium.

- Common: dizziness, feeling sick/vomiting, fatigue and blood tests may show raised levels of an enzyme that measures the muscle and heart function (creatine kinase enzyme). In patients with high blood pressure and type 2 diabetes with kidney disease, dizziness when getting up from a lying or sitting position, low blood pressure when getting up from a lying or sitting position, pain in joints or muscles and decreased levels of a protein in the red blood cells (haemoglobin) were also reported.

- Uncommon: heart rate increased, flushing, cough, diarrhoea, indigestion/heartburn, sexual dysfunction (problems with sexual performance), chest pain.

Some undesirable effects have been reported since marketing of Irbesartan BMS but the frequency for them to occur is not known. These undesirable effects are: headache, taste disturbance, ringing in the ears, muscle cramps, pain in joints and muscles, abnormal liver function, increased blood potassium

levels, impaired kidney function, and inflammation of small blood vessels mainly affecting the skin (a condition known as leukocytoclastic vasculitis).

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

## 5. HOW TO STORE IRBESARTAN BMS

Keep out of the reach and sight of children.

Do not use Irbesartan BMS 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 30°C.

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 BMS contains**

- The active substance is irbesartan. Each tablet of Irbesartan BMS 75 mg contains 75 mg irbesartan.
- The other ingredients are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hypromellose, silicon dioxide, magnesium stearate, titanium dioxide, macrogol 3000, carnauba wax.

**What Irbesartan BMS looks like and contents of the pack**

Irbesartan BMS 75 mg film-coated tablets are white to off-white, biconvex, and oval-shaped with a heart debossed on one side and the number 2871 engraved on the other side.

Irbesartan BMS 75 mg film-coated tablets are supplied in blister packs of 14, 28, 56, 84 or 98 film-coated tablets. Unidose blister packs of 56 x 1 film-coated tablet for delivery in hospitals are also available.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder:**
BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH - United Kingdom

**Manufacturer:**
SANOFI WINTHROP INDUSTRIE
1, rue de la Vierge
Ambarès & Lagrave
F-33565 Carbon Blanc Cedex - France

SANOFI SYNTHELABO LIMITED
Edgefield Avenue - Fawdon
Newcastle Upon Tyne, Tyne & Wear NE3 3TT - United Kingdom

SANOFI WINTHROP INDUSTRIE
30-36 Avenue Gustave Eiffel, BP 7166
F-37071 Tours Cedex 2 - France

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

**Belgique/België/Belgien**
BRISTOL-MYERS SQUIBB BELGIUM S.A./N.V.
Tél/Tel: + 32 2 352 74 60

**Luxembourg/Luxemburg**
BRISTOL-MYERS SQUIBB BELGIUM S.A./N.V.
Tél/Tel: + 32 2 352 74 60

**България**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Тел.: + 359 800 12 400

**Magyarország**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel.: + 36 1 301 9700

**Česká republika**
BRISTOL-MYERS SQUIBB SPOL. S R.O.
Tel: + 420 221 016 111

**Malta**
BRISTOL-MYERS SQUIBB S.R.L.
Tel: + 39 06 50 39 61

**Danmark**
BRISTOL-MYERS SQUIBB
Tlf: + 45 45 93 05 06

**Nederland**
BRISTOL-MYERS SQUIBB BV
Tel: + 31 34 857 42 22

**Deutschland**
BRISTOL-MYERS SQUIBB GMBH & CO. KGAA
Tel: + 49 89 121 42-0

**Norge**
BRISTOL-MYERS SQUIBB NORWAY LTD
Tlf: + 47 67 55 53 50

**Eesti**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 372 640 1301

**Österreich**
BRISTOL-MYERS SQUIBB GESMBH
Tel: + 43 1 60 14 30

**Ελλάδα**
BRISTOL-MYERS SQUIBB A.E.
Τηλ: + 30 210 6074300

**Polska**
BRISTOL-MYERS SQUIBB POLSKA SP. Z O.O.
Tel.: + 48 22 5796666

**España**
BRISTOL-MYERS SQUIBB, S.A.
Tel: + 34 91 456 53 00

**Portugal**
BRISTOL-MYERS SQUIBB FARMACÊUTICA
PORTUGUESA, S.A.
Tel: + 351 21 440 70 00

**France**
BRISTOL-MYERS SQUIBB SARL
Tél: + 33 (0)810 410 500

**România**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 40 (0)21 272 16 00

**Ireland**
BRISTOL-MYERS SQUIBB PHARMACEUTICALS LTD
Tel: + 353 (1 800) 749 749

**Slovenija**
BRISTOL-MYERS SQUIBB SPOL. S R.O.
Tel: + 386 1 236 47 00

**Ísland**
VISTOR HF
Sími: + 354 535 7000

**Slovenská republika**
BRISTOL-MYERS SQUIBB SPOL. S R.O.
Tel: + 421 2 59298411

**Italia**
BRISTOL-MYERS SQUIBB S.R.L.
Tel: + 39 06 50 39 61

**Suomi/Finland**
OY BRISTOL-MYERS SQUIBB (FINLAND) AB
Puh/Tel: + 358 9 251 21 230

**Κύπρος**
ΑΚΗΣ ΠΑΝΑΓΙΩΤΟΥ & ΥΙΟΣ Ε.Π.Ε.
Τηλ: + 357 22 677038

**Latvija**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 371 67 50 21 85

**Lietuva**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 370 5 2790 762

**Sverige**
BRISTOL-MYERS SQUIBB AB
Tel: + 46 8 704 71 00

**United Kingdom**
BRISTOL-MYERS SQUIBB PHARMACEUTICALS LTD
Tel: + 44 (0800) 731 1736

**This leaflet was last approved in**

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

**PACKAGE LEAFLET: INFORMATION FOR THE USER**
**Irbesartan BMS 150 mg film-coated tablets**
irbesartan

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

**In this leaflet:**




## 1. WHAT IRBESARTAN BMS IS AND WHAT IT IS USED FOR

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

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

## 2. BEFORE YOU TAKE IRBESARTAN BMS

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

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

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

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

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

Irbesartan BMS does not usually interact with other medicines.

**You may need to have blood checks if you take:**
- potassium supplements
- salt substitutes containing potassium
- potassium-sparing medicines (such as certain diuretics)
- medicines containing lithium

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

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

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

**Breast-feeding**
Tell your doctor if you are breast-feeding or about to start breast-feeding. Irbesartan BMS is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

**Driving and using machines**
No studies on the effects on the ability to drive and use machines have been performed. Irbesartan BMS is unlikely to affect your ability to drive or use machines. However, occasionally dizziness or weariness may occur during treatment of high blood pressure. If you experience these, talk to your doctor before attempting to drive or use machines.

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



## 3. HOW TO TAKE IRBESARTAN BMS

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

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

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

- **Patients with high blood pressure and type 2 diabetes with kidney disease**
  In patients with high blood pressure and type 2 diabetes, 300 mg (two tablets a day) once daily is the preferred maintenance dose for the treatment of associated kidney disease.

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

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

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

**Children should not take Irbesartan BMS**
Irbesartan BMS should not be given to children under 18 years of age. If a child swallows some tablets, contact your doctor immediately.

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

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

## 4. POSSIBLE SIDE EFFECTS

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

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

The frequency of the side effects listed below is defined using the following convention:
Very common: at least 1 in 10 patients or more
Common: at least 1 in 100 and less than 1 in 10 patients
Uncommon: at least 1 in 1000 and less than 1 in 100 patients

Side effects reported in clinical studies for patients treated with Irbesartan BMS were:
- Very common: if you suffer from high blood pressure and type 2 diabetes with kidney disease, blood tests may show an increased level of potassium.

- Common: dizziness, feeling sick/vomiting, fatigue and blood tests may show raised levels of an enzyme that measures the muscle and heart function (creatine kinase enzyme). In patients with high blood pressure and type 2 diabetes with kidney disease, dizziness when getting up from a lying or sitting position, low blood pressure when getting up from a lying or sitting position, pain in joints or muscles and decreased levels of a protein in the red blood cells (haemoglobin) were also reported.

- Uncommon: heart rate increased, flushing, cough, diarrhoea, indigestion/heartburn, sexual dysfunction (problems with sexual performance), chest pain.

Some undesirable effects have been reported since marketing of Irbesartan BMS but the frequency for them to occur is not known. These undesirable effects are: headache, taste disturbance, ringing in the ears, muscle cramps, pain in joints and muscles, abnormal liver function, increased blood potassium

levels, impaired kidney function, and inflammation of small blood vessels mainly affecting the skin (a condition known as leukocytoclastic vasculitis).

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

## 5. HOW TO STORE IRBESARTAN BMS

Keep out of the reach and sight of children.

Do not use Irbesartan BMS 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 30°C.

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 BMS contains**

- The active substance is irbesartan. Each tablet of Irbesartan BMS 150 mg contains 150 mg irbesartan.
- The other ingredients are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hypromellose, silicon dioxide, magnesium stearate, titanium dioxide, macrogol 3000, carnauba wax.

**What Irbesartan BMS looks like and contents of the pack**

Irbesartan BMS 150 mg film-coated tablets are white to off-white, biconvex, and oval-shaped with a heart debossed on one side and the number 2872 engraved on the other side.

Irbesartan BMS 150 mg film-coated tablets are supplied in blister packs of 14, 28, 56, 84 or 98 film-coated tablets. Unidose blister packs of 56 x 1 film-coated tablet for delivery in hospitals are also available.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder:**
BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH - United Kingdom

**Manufacturer:**
SANOFI WINTHROP INDUSTRIE
1, rue de la Vierge
Ambarès & Lagrave
F-33565 Carbon Blanc Cedex - France

SANOFI SYNTHELABO LIMITED
Edgefield Avenue - Fawdon
Newcastle Upon Tyne, Tyne & Wear NE3 3TT - United Kingdom

SANOFI WINTHROP INDUSTRIE
30-36 Avenue Gustave Eiffel, BP 7166
F-37071 Tours Cedex 2 - France

CHINOIN PRIVATE CO. LTD.
Lévai u.5.
2112 Veresegyház - Hungary

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

**Belgique/België/Belgien**
BRISTOL-MYERS SQUIBB BELGIUM S.A./N.V.
Tél/Tel: + 32 2 352 74 60

**България**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Тел.: + 359 800 12 400

**Česká republika**
BRISTOL-MYERS SQUIBB SPOL. S R.O.
Tel: + 420 221 016 111

**Danmark**
BRISTOL-MYERS SQUIBB
Tlf: + 45 45 93 05 06

**Deutschland**
BRISTOL-MYERS SQUIBB GMBH & CO. KGAA
Tel: + 49 89 121 42-0

**Eesti**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 372 640 1301

**Ελλάδα**
BRISTOL-MYERS SQUIBB A.E.
Τηλ: + 30 210 6074300

**España**
BRISTOL-MYERS SQUIBB, S.A.
Tel: + 34 91 456 53 00

**France**
BRISTOL-MYERS SQUIBB SARL
Tél: + 33 (0)810 410 500

**Ireland**
BRISTOL-MYERS SQUIBB PHARMACEUTICALS LTD
Tel: + 353 (1 800) 749 749

**Ísland**
VISTOR HF
Sími: + 354 535 7000

**Italia**
BRISTOL-MYERS SQUIBB S.R.L.
Tel: + 39 06 50 39 61

**Luxembourg/Luxemburg**
BRISTOL-MYERS SQUIBB BELGIUM S.A./N.V.
Tél/Tel: + 32 2 352 74 60

**Magyarország**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel.: + 36 1 301 9700

**Malta**
BRISTOL-MYERS SQUIBB S.R.L.
Tel: + 39 06 50 39 61

**Nederland**
BRISTOL-MYERS SQUIBB BV
Tel: + 31 34 857 42 22

**Norge**
BRISTOL-MYERS SQUIBB NORWAY LTD
Tlf: + 47 67 55 53 50

**Österreich**
BRISTOL-MYERS SQUIBB GESMBH
Tel: + 43 1 60 14 30

**Polska**
BRISTOL-MYERS SQUIBB POLSKA SP. Z O.O.
Tel.: + 48 22 5796666

**Portugal**
BRISTOL-MYERS SQUIBB FARMACÊUTICA
PORTUGUESA, S.A.
Tel: + 351 21 440 70 00

**România**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 40 (0)21 272 16 00

**Slovenija**
BRISTOL-MYERS SQUIBB SPOL. S R.O.
Tel: + 386 1 236 47 00

**Slovenská republika**
BRISTOL-MYERS SQUIBB SPOL. S R.O.
Tel: + 421 2 59298411

**Suomi/Finland**
OY BRISTOL-MYERS SQUIBB (FINLAND) AB
Puh/Tel: + 358 9 251 21 230

**Κύπρος**
ΑΚΗΣ ΠΑΝΑΓΙΩΤΟΥ & ΥΙΟΣ Ε.Π.Ε.
Τηλ: + 357 22 677038

**Latvija**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 371 67 50 21 85

**Lietuva**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 370 5 2790 762

**Sverige**
BRISTOL-MYERS SQUIBB AB
Tel: + 46 8 704 71 00

**United Kingdom**
BRISTOL-MYERS SQUIBB PHARMACEUTICALS LTD
Tel: + 44 (0800) 731 1736

**This leaflet was last approved in**

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

**PACKAGE LEAFLET: INFORMATION FOR THE USER**
**Irbesartan BMS 300 mg film-coated tablets**
irbesartan

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

**In this leaflet:**




## 1. WHAT IRBESARTAN BMS IS AND WHAT IT IS USED FOR

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

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

## 2. BEFORE YOU TAKE IRBESARTAN BMS

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

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

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

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

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

Irbesartan BMS does not usually interact with other medicines.

**You may need to have blood checks if you take:**
- potassium supplements
- salt substitutes containing potassium
- potassium-sparing medicines (such as certain diuretics)
- medicines containing lithium

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

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

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

**Breast-feeding**
Tell your doctor if you are breast-feeding or about to start breast-feeding. Irbesartan BMS is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

**Driving and using machines**
No studies on the effects on the ability to drive and use machines have been performed. Irbesartan BMS is unlikely to affect your ability to drive or use machines. However, occasionally dizziness or weariness may occur during treatment of high blood pressure. If you experience these, talk to your doctor before attempting to drive or use machines.

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



## 3. HOW TO TAKE IRBESARTAN BMS

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

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

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

- **Patients with high blood pressure and type 2 diabetes with kidney disease**
  In patients with high blood pressure and type 2 diabetes, 300 mg once daily is the preferred maintenance dose for the treatment of associated kidney disease.

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

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

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

**Children should not take Irbesartan BMS**
Irbesartan BMS should not be given to children under 18 years of age. If a child swallows some tablets, contact your doctor immediately.

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

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

## 4. POSSIBLE SIDE EFFECTS

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

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

The frequency of the side effects listed below is defined using the following convention:
Very common: at least 1 in 10 patients or more
Common: at least 1 in 100 and less than 1 in 10 patients
Uncommon: at least 1 in 1000 and less than 1 in 100 patients

Side effects reported in clinical studies for patients treated with Irbesartan BMS were:
- Very common: if you suffer from high blood pressure and type 2 diabetes with kidney disease, blood tests may show an increased level of potassium.

- Common: dizziness, feeling sick/vomiting, fatigue and blood tests may show raised levels of an enzyme that measures the muscle and heart function (creatine kinase enzyme). In patients with high blood pressure and type 2 diabetes with kidney disease, dizziness when getting up from a lying or sitting position, low blood pressure when getting up from a lying or sitting position, pain in joints or muscles and decreased levels of a protein in the red blood cells (haemoglobin) were also reported.

- Uncommon: heart rate increased, flushing, cough, diarrhoea, indigestion/heartburn, sexual dysfunction (problems with sexual performance), chest pain.

Some undesirable effects have been reported since marketing of Irbesartan BMS but the frequency for them to occur is not known. These undesirable effects are: headache, taste disturbance, ringing in the ears, muscle cramps, pain in joints and muscles, abnormal liver function, increased blood potassium

levels, impaired kidney function, and inflammation of small blood vessels mainly affecting the skin (a condition known as leukocytoclastic vasculitis).

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

## 5. HOW TO STORE IRBESARTAN BMS

Keep out of the reach and sight of children.

Do not use Irbesartan BMS 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 30°C.

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 BMS contains**

- The active substance is irbesartan. Each tablet of Irbesartan BMS 300 mg contains 300 mg irbesartan.
- The other ingredients are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hypromellose, silicon dioxide, magnesium stearate, titanium dioxide, macrogol 3000, carnauba wax.

**What Irbesartan BMS looks like and contents of the pack**
Irbesartan BMS 300 mg film-coated tablets are white to off-white, biconvex, and oval-shaped with a heart debossed on one side and the number 2873 engraved on the other side.

Irbesartan BMS 300 mg film-coated tablets are supplied in blister packs of 14, 28, 56, 84 or 98 film-coated tablets. Unidose blister packs of 56 x 1 film-coated tablet for delivery in hospitals are also available.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder:**
BRISTOL-MYERS SQUIBB PHARMA EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH - United Kingdom

**Manufacturer:**
SANOFI WINTHROP INDUSTRIE
1, rue de la Vierge
Ambarès & Lagrave
F-33565 Carbon Blanc Cedex - France

SANOFI SYNTHELABO LIMITED
Edgefield Avenue - Fawdon
Newcastle Upon Tyne, Tyne & Wear NE3 3TT - United Kingdom

SANOFI WINTHROP INDUSTRIE
30-36 Avenue Gustave Eiffel, BP 7166
F-37071 Tours Cedex 2 - France

CHINOIN PRIVATE CO. LTD.
Lévai u.5.
2112 Veresegyház - Hungary

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

**Belgique/België/Belgien**
BRISTOL-MYERS SQUIBB BELGIUM S.A./N.V.
Tél/Tel: + 32 2 352 74 60

**Luxembourg/Luxemburg**
BRISTOL-MYERS SQUIBB BELGIUM S.A./N.V.
Tél/Tel: + 32 2 352 74 60

**България**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Тел.: + 359 800 12 400

**Magyarország**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel.: + 36 1 301 9700

**Česká republika**
BRISTOL-MYERS SQUIBB SPOL. S R.O.
Tel: + 420 221 016 111

**Malta**
BRISTOL-MYERS SQUIBB S.R.L.
Tel: + 39 06 50 39 61

**Danmark**
BRISTOL-MYERS SQUIBB
Tlf: + 45 45 93 05 06

**Nederland**
BRISTOL-MYERS SQUIBB BV
Tel: + 31 34 857 42 22

**Deutschland**
BRISTOL-MYERS SQUIBB GMBH & CO. KGAA
Tel: + 49 89 121 42-0

**Norge**
BRISTOL-MYERS SQUIBB NORWAY LTD
Tlf: + 47 67 55 53 50

**Eesti**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 372 640 1301

**Österreich**
BRISTOL-MYERS SQUIBB GESMBH
Tel: + 43 1 60 14 30

**Ελλάδα**
BRISTOL-MYERS SQUIBB A.E.
Τηλ: + 30 210 6074300

**Polska**
BRISTOL-MYERS SQUIBB POLSKA SP. Z O.O.
Tel.: + 48 22 5796666

**España**
BRISTOL-MYERS SQUIBB, S.A.
Tel: + 34 91 456 53 00

**Portugal**
BRISTOL-MYERS SQUIBB FARMACÊUTICA
PORTUGUESA, S.A.
Tel: + 351 21 440 70 00

**France**
BRISTOL-MYERS SQUIBB SARL
Tél: + 33 (0)810 410 500

**România**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 40 (0)21 272 16 00

**Ireland**
BRISTOL-MYERS SQUIBB PHARMACEUTICALS LTD
Tel: + 353 (1 800) 749 749

**Slovenija**
BRISTOL-MYERS SQUIBB SPOL. S R.O.
Tel: + 386 1 236 47 00

**Ísland**
VISTOR HF
Sími: + 354 535 7000

**Slovenská republika**
BRISTOL-MYERS SQUIBB SPOL. S R.O.
Tel: + 421 2 59298411

**Italia**
BRISTOL-MYERS SQUIBB S.R.L.
Tel: + 39 06 50 39 61

**Suomi/Finland**
OY BRISTOL-MYERS SQUIBB (FINLAND) AB
Puh/Tel: + 358 9 251 21 230

**Κύπρος**
ΑΚΗΣ ΠΑΝΑΓΙΩΤΟΥ & ΥΙΟΣ Ε.Π.Ε.
Τηλ: + 357 22 677038

**Latvija**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 371 67 50 21 85

**Lietuva**
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 370 5 2790 762

**Sverige**
BRISTOL-MYERS SQUIBB AB
Tel: + 46 8 704 71 00

**United Kingdom**
BRISTOL-MYERS SQUIBB PHARMACEUTICALS LTD
Tel: + 44 (0800) 731 1736

**This leaflet was last approved in**

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/