**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg tablets.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 150 mg of irbesartan and 12.5 mg of hydrochlorothiazide.

Excipient:
Each tablet contains 26.65 mg of lactose (as lactose monohydrate).

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet.
Peach, biconvex, oval-shaped, with a heart debossed on one side and the number 2775 engraved on the other side.



## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment of essential hypertension.
This fixed dose combination is indicated in adult patients whose blood pressure is not adequately controlled on irbesartan or hydrochlorothiazide alone (see section 5.1).

### 4.2 Posology and method of administration

Irbesartan Hydrochlorothiazide BMS can be taken once daily, with or without food.
Dose titration with the individual components (i.e. irbesartan and hydrochlorothiazide) may be recommended.

When clinically appropriate, direct change from monotherapy to the fixed combinations may be considered:

- Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg may be administered in patients whose blood pressure is not adequately controlled with hydrochlorothiazide or irbesartan 150 mg alone;
- Irbesartan Hydrochlorothiazide BMS 300 mg/12.5 mg may be administered in patients insufficiently controlled by irbesartan 300 mg or by Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg.
- Irbesartan Hydrochlorothiazide BMS 300 mg/25 mg may be administered in patients insufficiently controlled by Irbesartan Hydrochlorothiazide BMS 300 mg/12.5 mg.

Doses higher than 300 mg irbesartan/25 mg hydrochlorothiazide once daily are not recommended.
When necessary, Irbesartan Hydrochlorothiazide BMS may be administered with another antihypertensive medicinal product (see section 4.5).

Renal impairment: due to the hydrochlorothiazide component, Irbesartan Hydrochlorothiazide BMS is not recommended for patients with severe renal dysfunction (creatinine clearance < 30 ml/min). Loop diuretics are preferred to thiazides in this population. No dosage adjustment is necessary in patients with renal impairment whose renal creatinine clearance is ≥ 30 ml/min (see sections 4.3 and 4.4).

Hepatic impairment: Irbesartan Hydrochlorothiazide BMS is not indicated in patients with severe hepatic impairment. Thiazides should be used with caution in patients with impaired hepatic function. No dosage adjustment of Irbesartan Hydrochlorothiazide BMS is necessary in patients with mild to moderate hepatic impairment (see section 4.3).

Elderly patients: no dosage adjustment of Irbesartan Hydrochlorothiazide BMS is necessary in elderly patients.

Paediatric patients: Irbesartan Hydrochlorothiazide BMS is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

## 4.3 Contraindications

- Hypersensitivity to the active substances, to any of the excipients (see section 6.1), or to other sulfonamide-derived substances (hydrochlorothiazide is a sulfonamide-derived substance)
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)
- Severe renal impairment (creatinine clearance < 30 ml/min)
- Refractory hypokalaemia, hypercalcaemia
- Severe hepatic impairment, biliary cirrhosis and cholestasis

## 4.4 Special warnings and precautions for use

Hypotension - Volume-depleted patients: Irbesartan Hydrochlorothiazide BMS has been rarely associated with symptomatic hypotension in hypertensive patients without other risk factors for hypotension. Symptomatic hypotension may be expected to 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 initiating therapy with Irbesartan Hydrochlorothiazide BMS.

Renal artery stenosis - 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 angiotensin converting enzyme inhibitors or angiotensin-II receptor antagonists. While this is not documented with Irbesartan Hydrochlorothiazide BMS, a similar effect should be anticipated.

Renal impairment and kidney transplantation: when Irbesartan Hydrochlorothiazide BMS is used in patients with impaired renal function, a periodic monitoring of potassium, creatinine and uric acid serum levels is recommended. There is no experience regarding the administration of Irbesartan Hydrochlorothiazide BMS in patients with a recent kidney transplantation. Irbesartan Hydrochlorothiazide BMS should not be used in patients with severe renal impairment (creatinine clearance < 30 ml/min) (see section 4.3). Thiazide diuretic-associated azotemia may occur in patients with impaired renal function. No dosage adjustment is necessary in patients with renal impairment whose creatinine clearance is ≥ 30 ml/min. However, in patients with mild to moderate renal impairment (creatinine clearance ≥ 30 ml/min but < 60 ml/min) this fixed dose combination should be administered with caution.

Hepatic impairment: thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. There is no clinical experience with Irbesartan Hydrochlorothiazide BMS in patients with hepatic impairment.

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 Hydrochlorothiazide BMS is not recommended.

Metabolic and endocrine effects: thiazide therapy may impair glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Latent diabetes mellitus may become manifest during thiazide therapy.
Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy; however at the 12.5 mg dose contained in Irbesartan Hydrochlorothiazide BMS, minimal or no effects were reported.
Hyperuricaemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Electrolyte imbalance: as for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.
Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloremic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting.
Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with irbesartan may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH. Conversely, due to the irbesartan component of Irbesartan Hydrochlorothiazide BMS hyperkalaemia might occur, especially in the presence of renal impairment and/or heart failure, and diabetes mellitus. Adequate monitoring of serum potassium in patients at risk is recommended. Potassium-sparing diuretics, potassium supplements or potassium-containing salts substitutes should be co-administered cautiously with Irbesartan Hydrochlorothiazide BMS (see section 4.5).
There is no evidence that irbesartan would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.
Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.
Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnaesemia.

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

Anti-doping test: hydrochlorothiazide contained in this medicinal product could produce a positive analytic result in an anti-doping test.

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, azotemia, oliguria, or rarely acute renal failure. As with any antihypertensive agent, excessive blood pressure decrease in patients with ischemic cardiopathy or ischemic cardiovascular disease could result in a myocardial infarction or stroke.
Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.
Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics.
Cases of photosensitivity reactions have been reported with thiazides diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

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.

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

Other antihypertensive agents: the antihypertensive effect of Irbesartan Hydrochlorothiazide BMS may be increased with the concomitant use of other antihypertensive agents. Irbesartan and hydrochlorothiazide (at doses up to 300 mg irbesartan/25 mg hydrochlorothiazide) have been safely administered with other antihypertensive agents including calcium channel blockers and beta-adrenergic blockers. Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with irbesartan with or without thiazide diuretics unless the volume depletion is corrected first (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. Furthermore, renal clearance of lithium is reduced by thiazides so the risk of lithium toxicity could be increased with Irbesartan Hydrochlorothiazide BMS. Therefore, the combination of lithium and Irbesartan Hydrochlorothiazide BMS is not recommended (see section 4.4). If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Medicinal products affecting potassium: the potassium-depleting effect of hydrochlorothiazide is attenuated by the potassium-sparing effect of irbesartan. However, this effect of hydrochlorothiazide on serum potassium would be expected to be potentiated by other medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, penicillin G sodium). Conversely, based on the experience with the use of other medicinal products that blunt 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 sodium) may lead to increases in serum potassium. Adequate monitoring of serum potassium in patients at risk is recommended (see section 4.4).



Medicinal products affected by serum potassium disturbances: periodic monitoring of serum potassium is recommended when Irbesartan Hydrochlorothiazide BMS is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics).

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

Additional information on irbesartan interactions: in clinical studies, the pharmacokinetic of irbesartan is not affected by hydrochlorothiazide. Irbesartan is mainly metabolised by CYP2C9 and to a lesser

extent by glucuronidation. No significant pharmacokinetic or pharmacodynamic interactions were observed when irbesartan was coadministered with warfarin, a medicinal product metabolised by CYP2C9. The effects of CYP2C9 inducers such as rifampicin on the pharmacokinetic of irbesartan have not been evaluated. The pharmacokinetic of digoxin was not altered by co-administration of irbesartan.

Additional information on hydrochlorothiazide interactions: when administered concurrently, the following medicinal products may interact with thiazide diuretics:

*Alcohol:* potentiation of orthostatic hypotension may occur;

*Antidiabetic medicinal products (oral agents and insulins):* dosage adjustment of the antidiabetic medicinal product may be required (see section 4.4);

*Colestyramine and Colestipol resins:* absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins;

*Corticosteroids, ACTH:* electrolyte depletion, particularly hypokalaemia, may be increased;

*Digitalis glycosides:* thiazide induced hypokalaemia or hypomagnaesemia favour the onset of digitalis-induced cardiac arrhythmias (see section 4.4);

*Non-steroidal anti-inflammatory drugs:* the administration of a non-steroidal anti-inflammatory drug may reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics in some patients;

*Pressor amines (e.g. noradrenaline):* the effect of pressor amines may be decreased, but not sufficiently to preclude their use;

*Nondepolarizing skeletal muscle relaxants (e.g. tubocurarine):* the effect of nondepolarizing skeletal muscle relaxants may be potentiated by hydrochlorothiazide;

*Antigout medicinal products:* dosage adjustments of antigout medicinal products may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol;

*Calcium salts:* thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements or calcium sparing medicinal products (e.g. vitamin D therapy) must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly;

*Other interactions:* the hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides. Anticholinergic agents (e.g. atropine, beperiden) may increase the bioavailability of thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate. Thiazides may increase the risk of adverse effects caused by amantadine. Thiazides may reduce the renal excretion of cytotoxic medicinal products (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.



### 4.6 Pregnancy and lactation

Pregnancy:

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|---|
| 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).

Thiazides cross the placental barrier and appear in cord blood. They may cause a decrease in placental perfusion, foetal electrolyte disturbances and possibly other reactions that have occurred in the adults. Cases of neonatal thrombocytopenia, or foetal or neonatal jaundice have been reported with maternal thiazide therapy. Since Irbesartan Hydrochlorothiazide BMS contains hydrochlorothiazide, it is not recommended during the first trimester of pregnancy. A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy.



Lactation:

Because no information is available regarding the use of Irbesartan Hydrochlorothiazide BMS during breast-feeding, Irbesartan Hydrochlorothiazide 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 Hydrochlorothiazide BMS is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur during treatment of hypertension.

### 4.8 Undesirable effects

Irbesartan/hydrochlorothiazide combination:
Table 1 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled trials in which 898 hypertensive patients received various doses (range: 37.5 mg/6.25 mg to 300 mg/25 mg irbesartan/hydrochlorothiazide).

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

**Table 1:** Adverse Reactions in Placebo-Controlled Trials and Spontaneous Reports*

| | | |
|---|---|---|
| *Investigations:* | Common: | increases in blood urea nitrogen (BUN), creatinine and creatine kinase |
| | Uncommon: | decreases in serum potassium and sodium |
| *Cardiac disorders:* | Uncommon: | syncope, hypotension, tachycardia, oedema |
| *Nervous system disorders:* | Common: | dizziness |
| | Uncommon: | orthostatic dizziness |

| | | |
|---|---|---|
| | Not known: | headache |
| *Ear and labyrinth disorders:* | Not known: | tinnitus |
| *Respiratory, thoracic and mediastinal disorders:* | Not known: | cough |
| *Gastrointestinal disorders:* | Common:<br>Uncommon:<br>Not known: | nausea/vomiting<br>diarrhoea<br>dyspepsia, dysgeusia |
| *Renal and urinary disorders:* | Common:<br>Not known: | abnormal urination<br>impaired renal function including isolated cases of renal failure in patients at risk (see section 4.4) |
| *Musculoskeletal and connective tissue disorders:* | Uncommon:<br>Not known: | swelling extremity<br>arthralgia, myalgia |
| *Metabolism and nutrition disorders:* | Not known: | hyperkalaemia |
| *Vascular disorders:* | Uncommon: | flushing |
| *General disorders and administration site conditions:* | Common: | fatigue |
| *Immune system disorders:* | Not known: | cases of hypersensitivity reactions such as angioedema, rash, urticaria |
| *Hepatobiliary disorders:* | Not known: | hepatitis, abnormal liver function |
| *Reproductive system and breast disorders:* | Uncommon: | sexual dysfunction, libido changes |

* Frequency for adverse reactions detected by spontaneous reports is described as "not known"

Additional information on individual components: in addition to the adverse reactions listed above for the combination product, other adverse reactions previously reported with one of the individual components may be potential adverse reactions with Irbesartan Hydrochlorothiazide BMS. Tables 2 and 3 below detail the adverse reactions reported with the individual components of Irbesartan Hydrochlorothiazide BMS.

**Table 2:** Adverse reactions reported with the use of **irbesartan** alone

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

**Table 3:** Adverse reactions (regardless of relationship to medicinal product) reported with the use of **hydrochlorothiazide** alone

| | | |
|---|---|---|
| *Investigations:* | Not known: | electrolyte imbalance (including hypokalaemia and hyponatraemia, see section 4.4), hyperuricaemia, glycosuria, hyperglycaemia, increases in cholesterol and triglycerides |
| *Cardiac disorders:* | Not known: | cardiac arrhythmias |
| *Blood and lymphatic system disorders:* | Not known: | aplastic anaemia, bone marrow depression, neutropenia/agranulocytosis, haemolytic anaemia, leucopenia, thrombocytopenia |
| *Nervous system disorders:* | Not known: | vertigo, paraesthesia, light-headedness, restlessness |
| *Eye disorders:* | Not known: | transient blurred vision, xanthopsia |
| *Respiratory, thoracic and mediastinal disorders:* | Not known: | respiratory distress (including pneumonitis and pulmonary oedema) |
| *Gastrointestinal disorders:* | Not known: | pancreatitis, anorexia, diarrhoea, constipation, gastric irritation, sialadenitis, loss of appetite |
| *Renal and urinary disorders:* | Not known: | interstitial nephritis, renal dysfunction |

| | | |
|---|---|---|
| *Skin and subcutaneous tissue disorders:* | Not known: | anaphylactic reactions, toxic epidermal necrolysis, necrotizing angitis (vasculitis, cutaneous vasculitis), cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, photosensitivity reactions, rash, urticaria |
| *Musculoskeletal and connective tissue disorders:* | Not known: | weakness, muscle spasm |
| *Vascular disorders:* | Not known: | postural hypotension |
| *General disorders and administration site conditions:* | Not known: | fever |
| *Hepatobiliary disorders:* | Not known: | jaundice (intrahepatic cholestatic jaundice) |
| *Psychiatric disorders:* | Not known: | depression, sleep disturbances |

The dose dependent adverse events of hydrochlorothiazide (particularly electrolyte disturbances) may increase when titrating the hydrochlorothiazide.

### 4.9 Overdose

No specific information is available on the treatment of overdose with Irbesartan Hydrochlorothiazide BMS. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and/or gastric lavage. Activated charcoal may be useful in the treatment of overdose. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacements given quickly.

The most likely manifestations of irbesartan overdose are expected to be hypotension and tachycardia; bradycardia might also occur.

Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloremia, hyponatraemia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasms and/or accentuate cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic medicinal products.

Irbesartan is not removed by haemodialysis. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.



## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: angiotensin-II antagonists, combinations
ATC code: C09DA04.

Irbesartan Hydrochlorothiazide BMS is a combination of an angiotensin-II receptor antagonist, irbesartan, and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Irbesartan is a potent, orally active, selective angiotensin-II receptor ($AT_1$ subtype) 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 in patients without risk of electrolyte imbalance (see sections 4.4 and 4.5). 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.

Hydrochlorothiazide is a thiazide diuretic. The mechanism of antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity, increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. Presumably through blockade of the renin-angiotensin-aldosterone system, co-administration of irbesartan tends to reverse the potassium loss associated with these diuretics. With hydrochlorothiazide, onset of diuresis occurs in 2 hours, and peak effect occurs at about 4 hours, while the action persists for approximately 6-12 hours.

The combination of hydrochlorothiazide and irbesartan produces dose-related additive reductions in blood pressure across their therapeutic dose ranges. The addition of 12.5 mg hydrochlorothiazide to 300 mg irbesartan once daily in patients not adequately controlled on 300 mg irbesartan alone resulted in further placebo-corrected diastolic blood pressure reductions at trough (24 hours post-dosing) of 6.1 mm Hg. The combination of 300 mg irbesartan and 12.5 mg hydrochlorothiazide resulted in an overall placebo-subtracted systolic/diastolic reductions of up to 13.6/11.5 mm Hg.

Limited clinical data (7 out of 22 patients) suggest that patients not controlled with the 300 mg/12.5 mg combination may respond when uptitrated to 300 mg/25 mg. In these patients, an incremental blood pressure lowering effect was observed for both systolic blood pressure (SBP) and diastolic blood pressure (DBP) (13.3 and 8.3 mm Hg, respectively).

Once daily dosing with 150 mg irbesartan and 12.5 mg hydrochlorothiazide gave systolic/diastolic mean placebo-adjusted blood pressure reductions at trough (24 hours post-dosing) of 12.9/6.9 mm Hg in patients with mild-to-moderate hypertension. Peak effects occurred at 3-6 hours. When assessed by ambulatory blood pressure monitoring, the combination 150 mg irbesartan and 12.5 mg hydrochlorothiazide once daily produced consistent reduction in blood pressure over the 24 hours period with mean 24-hour placebo-subtracted systolic/diastolic reductions of 15.8/10.0 mm Hg. When measured by ambulatory blood pressure monitoring, the trough to peak effects of Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg were 100%. The trough to peak effects measured by cuff during office visits were 68% and 76% for Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg and Irbesartan Hydrochlorothiazide BMS 300 mg/12.5 mg, respectively. These 24-hour effects were observed without excessive blood pressure lowering at peak and are consistent with safe and effective blood-pressure lowering over the once-daily dosing interval.



In patients not adequately controlled on 25 mg hydrochlorothiazide alone, the addition of irbesartan gave an added placebo-subtracted systolic/diastolic mean reduction of 11.1/7.2 mm Hg.

The blood pressure lowering effect of irbesartan in combination with hydrochlorothiazide is apparent after the first dose and substantially present within 1-2 weeks, with the maximal effect occurring by 6-8 weeks. In long-term follow-up studies, the effect of irbesartan/hydrochlorothiazide was maintained for over one year. Although not specifically studied with the Irbesartan Hydrochlorothiazide BMS, rebound hypertension has not been seen with either irbesartan or hydrochlorothiazide.

The effect of the combination of irbesartan and hydrochlorothiazide on morbidity and mortality has not been studied. Epidemiological studies have shown that long term treatment with hydrochlorothiazide reduces the risk of cardiovascular mortality and morbidity.

There is no difference in response to Irbesartan Hydrochlorothiazide BMS, regardless of 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 non-black patients.

Efficacy and safety of Irbesartan Hydrochlorothiazide BMS as initial therapy for severe hypertension (defined as SeDBP ≥ 110 mmHg) was evaluated in a multicenter, randomized, double-blind, active-controlled, 8-week, parallel-arm study. A total of 697 patients were randomized in a 2:1 ratio to either irbesartan/hydrochlorothiazide 150 mg/12.5 mg or to irbesartan 150 mg and systematically force-titrated (before assessing the response to the lower dose) after one week to irbesartan/hydrochlorothiazide 300 mg/25 mg or irbesartan 300 mg, respectively.

The study recruited 58% males. The mean age of patients was 52.5 years, 13% were ≥ 65 years of age, and just 2% were ≥ 75 years of age. Twelve percent (12%) of patients were diabetic, 34% were hyperlipidemic and the most frequent cardiovascular condition was stable angina pectoris in 3.5% of the participants.

The primary objective of this study was to compare the proportion of patients whose SeDBP was controlled (SeDBP < 90 mmHg) at Week 5 of treatment. Forty-seven percent (47.2%) of patients on the combination achieved trough SeDBP < 90 mmHg compared to 33.2% of patients on irbesartan ($p = 0.0005$). The mean baseline blood pressure was approximately 172/113 mmHg in each treatment group and decreases of SeSBP/SeDBP at five weeks were 30.8/24.0 mmHg and 21.1/19.3 mmHg for irbesartan/hydrochlorothiazide and irbesartan, respectively ($p < 0.0001$).

The types and incidences of adverse events reported for patients treated with the combination were similar to the adverse event profile for patients on monotherapy. During the 8-week treatment period, there were no reported cases of syncope in either treatment group. There were 0.6% and 0% of patients with hypotension and 2.8% and 3.1% of patients with dizziness as adverse reactions reported in the combination and monotherapy groups, respectively.



## 5.2 Pharmacokinetic properties

Concomitant administration of hydrochlorothiazide and irbesartan has no effect on the pharmacokinetics of either medicinal product.

Irbesartan and hydrochlorothiazide are orally active agents and do not require biotransformation for their activity. Following oral administration of Irbesartan Hydrochlorothiazide BMS, the absolute oral bioavailability is 60-80% and 50-80% for irbesartan and hydrochlorothiazide, respectively. Food does not affect the bioavailability of Irbesartan Hydrochlorothiazide BMS. Peak plasma concentration occurs at 1.5-2 hours after oral administration for irbesartan and 1-2.5 hours for hydrochlorothiazide.

Plasma protein binding of irbesartan is approximately 96%, with negligible binding to cellular blood components. The volume of distribution for irbesartan is 53-93 litres. Hydrochlorothiazide is 68% protein-bound in the plasma, and its apparent volume of distribution is 0.83-1.14 l/kg.

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 was observed; the mechanism for this is unknown. The total body and renal clearance are 157-176 and 3.0-3.5 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. The mean plasma half-life of hydrochlorothiazide reportedly ranges from 5-15 hours.

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 and its metabolites are eliminated by both biliary and renal pathways. After either oral or intravenous 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. Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidneys. At least 61% of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier, and is excreted in breast milk.

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. In patients with creatinine clearance < 20 ml/min, the elimination half-life of hydrochlorothiazide was reported to increase to 21 hours.

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

Irbesartan/hydrochlorothiazide: the potential toxicity of the irbesartan/hydrochlorothiazide combination after oral administration was evaluated in rats and macaques in studies lasting up to 6 months. There were no toxicological findings observed of relevance to human therapeutic use. The following changes, observed in rats and macaques receiving the irbesartan/hydrochlorothiazide combination at 10/10 and 90/90 mg/kg/day, were also seen with one of the two medicinal products alone and/or were secondary to decreases in blood pressure (no significant toxicologic interactions were observed):

- kidney changes, characterized by slight increases in serum urea and creatinine, and hyperplasia/hypertrophy of the juxtaglomerular apparatus, which are a direct consequence of the interaction of irbesartan with the renin-angiotensin system;
- slight decreases in erythrocyte parameters (erythrocytes, haemoglobin, haematocrit);
- stomach discoloration, ulcers and focal necrosis of gastric mucosa were observed in few rats in a 6 months toxicity study at irbesartan 90 mg/kg/day, hydrochlorothiazide 90 mg/kg/day, and irbesartan/hydrochlorothiazide 10/10 mg/kg/day. These lesions were not observed in macaques;
- decreases in serum potassium due to hydrochlorothiazide and partly prevented when hydrochlorothiazide was given in combination with irbesartan.

Most of the above mentioned effects appear to be due to the pharmacological activity of irbesartan (blockade of angiotensin-II-induced inhibition of renin release, with stimulation of the renin-producing cells) and occur also with angiotensin converting enzyme inhibitors. These findings appear to have no relevance to the use of therapeutic doses of irbesartan/hydrochlorothiazide in humans.

No teratogenic effects were seen in rats given irbesartan and hydrochlorothiazide in combination at doses that produced maternal toxicity. The effects of the irbesartan/hydrochlorothiazide combination on fertility have not been evaluated in animal studies, as there is no evidence of adverse effect on fertility in animals or humans with either irbesartan or hydrochlorothiazide when administered alone. However, another angiotensin-II antagonist affected fertility parameters in animal studies when given alone. These findings were also observed with lower doses of this other angiotensin-II antagonist when given in combination with hydrochlorothiazide.

There was no evidence of mutagenicity or clastogenicity with the irbesartan/hydrochlorothiazide combination. The carcinogenic potential of irbesartan and hydrochlorothiazide in combination has not been evaluated in animal studies.

Irbesartan: 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 kidneys (such as interstitial nephritis, tubular distention, 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 was noted at doses causing significant maternal toxicity, including mortality. No teratogenic effects were observed in the rat or rabbit.

Hydrochlorothiazide: although equivocal evidence for a genotoxic or carcinogenic effect was found in some experimental models, the extensive human experience with hydrochlorothiazide has failed to show an association between its use and an increase in neoplasms.



## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Microcrystalline cellulose
Croscarmellose sodium
Lactose monohydrate
Magnesium stearate
Colloidal hydrated silica
Pregelatinised maize starch
Red and yellow ferric oxides (E172)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from moisture.

### 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 tablets; 7 blister cards of 8 x 1 tablets 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/1/06/369/001-005

## 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 Hydrochlorothiazide BMS 300 mg/12.5 mg tablets.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 300 mg of irbesartan and 12.5 mg of hydrochlorothiazide.

Excipient:
Each tablet contains 65.8 mg of lactose (as lactose monohydrate).

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet.
Peach, biconvex, oval-shaped, with a heart debossed on one side and the number 2776 engraved on the other side.



## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment of essential hypertension.
This fixed dose combination is indicated in adult patients whose blood pressure is not adequately controlled on irbesartan or hydrochlorothiazide alone (see section 5.1).

### 4.2 Posology and method of administration

Irbesartan Hydrochlorothiazide BMS can be taken once daily, with or without food.
Dose titration with the individual components (i.e. irbesartan and hydrochlorothiazide) may be recommended.

When clinically appropriate, direct change from monotherapy to the fixed combinations may be considered:

- Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg may be administered in patients whose blood pressure is not adequately controlled with hydrochlorothiazide or irbesartan 150 mg alone;
- Irbesartan Hydrochlorothiazide BMS 300 mg/12.5 mg may be administered in patients insufficiently controlled by irbesartan 300 mg or by Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg.
- Irbesartan Hydrochlorothiazide BMS 300 mg/25 mg may be administered in patients insufficiently controlled by Irbesartan Hydrochlorothiazide BMS 300 mg/12.5 mg.

Doses higher than 300 mg irbesartan/25 mg hydrochlorothiazide once daily are not recommended.
When necessary, Irbesartan Hydrochlorothiazide BMS may be administered with another antihypertensive medicinal product (see section 4.5).

Renal impairment: due to the hydrochlorothiazide component, Irbesartan Hydrochlorothiazide BMS is not recommended for patients with severe renal dysfunction (creatinine clearance < 30 ml/min). Loop diuretics are preferred to thiazides in this population. No dosage adjustment is necessary in patients with renal impairment whose renal creatinine clearance is ≥ 30 ml/min (see sections 4.3 and 4.4).

Hepatic impairment: Irbesartan Hydrochlorothiazide BMS is not indicated in patients with severe hepatic impairment. Thiazides should be used with caution in patients with impaired hepatic function. No dosage adjustment of Irbesartan Hydrochlorothiazide BMS is necessary in patients with mild to moderate hepatic impairment (see section 4.3).

Elderly patients: no dosage adjustment of Irbesartan Hydrochlorothiazide BMS is necessary in elderly patients.

Paediatric patients: Irbesartan Hydrochlorothiazide BMS is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

## 4.3 Contraindications

- Hypersensitivity to the active substances, to any of the excipients (see section 6.1), or to other sulfonamide-derived substances (hydrochlorothiazide is a sulfonamide-derived substance)
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)
- Severe renal impairment (creatinine clearance < 30 ml/min)
- Refractory hypokalaemia, hypercalcaemia
- Severe hepatic impairment, biliary cirrhosis and cholestasis

## 4.4 Special warnings and precautions for use

Hypotension - Volume-depleted patients: Irbesartan Hydrochlorothiazide BMS has been rarely associated with symptomatic hypotension in hypertensive patients without other risk factors for hypotension. Symptomatic hypotension may be expected to 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 initiating therapy with Irbesartan Hydrochlorothiazide BMS.

Renal artery stenosis - 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 angiotensin converting enzyme inhibitors or angiotensin-II receptor antagonists. While this is not documented with Irbesartan Hydrochlorothiazide BMS, a similar effect should be anticipated.

Renal impairment and kidney transplantation: when Irbesartan Hydrochlorothiazide BMS is used in patients with impaired renal function, a periodic monitoring of potassium, creatinine and uric acid serum levels is recommended. There is no experience regarding the administration of Irbesartan Hydrochlorothiazide BMS in patients with a recent kidney transplantation. Irbesartan Hydrochlorothiazide BMS should not be used in patients with severe renal impairment (creatinine clearance < 30 ml/min) (see section 4.3). Thiazide diuretic-associated azotemia may occur in patients with impaired renal function. No dosage adjustment is necessary in patients with renal impairment whose creatinine clearance is ≥ 30 ml/min. However, in patients with mild to moderate renal impairment (creatinine clearance ≥ 30 ml/min but < 60 ml/min) this fixed dose combination should be administered with caution.

Hepatic impairment: thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. There is no clinical experience with Irbesartan Hydrochlorothiazide BMS in patients with hepatic impairment.

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 Hydrochlorothiazide BMS is not recommended.

Metabolic and endocrine effects: thiazide therapy may impair glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Latent diabetes mellitus may become manifest during thiazide therapy.
Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy; however at the 12.5 mg dose contained in Irbesartan Hydrochlorothiazide BMS, minimal or no effects were reported.
Hyperuricaemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Electrolyte imbalance: as for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.
Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloremic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting.
Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with irbesartan may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH. Conversely, due to the irbesartan component of Irbesartan Hydrochlorothiazide BMS hyperkalaemia might occur, especially in the presence of renal impairment and/or heart failure, and diabetes mellitus. Adequate monitoring of serum potassium in patients at risk is recommended. Potassium-sparing diuretics, potassium supplements or potassium-containing salts substitutes should be co-administered cautiously with Irbesartan Hydrochlorothiazide BMS (see section 4.5).
There is no evidence that irbesartan would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.
Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.
Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnaesemia.

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

Anti-doping test: hydrochlorothiazide contained in this medicinal product could produce a positive analytic result in an anti-doping test.

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, azotemia, oliguria, or rarely acute renal failure. As with any antihypertensive agent, excessive blood pressure decrease in patients with ischemic cardiopathy or ischemic cardiovascular disease could result in a myocardial infarction or stroke.
Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.
Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics.
Cases of photosensitivity reactions have been reported with thiazides diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

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.

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

Other antihypertensive agents: the antihypertensive effect of Irbesartan Hydrochlorothiazide BMS may be increased with the concomitant use of other antihypertensive agents. Irbesartan and hydrochlorothiazide (at doses up to 300 mg irbesartan/25 mg hydrochlorothiazide) have been safely administered with other antihypertensive agents including calcium channel blockers and beta-adrenergic blockers. Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with irbesartan with or without thiazide diuretics unless the volume depletion is corrected first (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. Furthermore, renal clearance of lithium is reduced by thiazides so the risk of lithium toxicity could be increased with Irbesartan Hydrochlorothiazide BMS. Therefore, the combination of lithium and Irbesartan Hydrochlorothiazide BMS is not recommended (see section 4.4). If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Medicinal products affecting potassium: the potassium-depleting effect of hydrochlorothiazide is attenuated by the potassium-sparing effect of irbesartan. However, this effect of hydrochlorothiazide on serum potassium would be expected to be potentiated by other medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, penicillin G sodium). Conversely, based on the experience with the use of other medicinal products that blunt 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 sodium) may lead to increases in serum potassium. Adequate monitoring of serum potassium in patients at risk is recommended (see section 4.4).



Medicinal products affected by serum potassium disturbances: periodic monitoring of serum potassium is recommended when Irbesartan Hydrochlorothiazide BMS is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics).

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

Additional information on irbesartan interactions: in clinical studies, the pharmacokinetic of irbesartan is not affected by hydrochlorothiazide. Irbesartan is mainly metabolised by CYP2C9 and to a lesser

extent by glucuronidation. No significant pharmacokinetic or pharmacodynamic interactions were observed when irbesartan was coadministered with warfarin, a medicinal product metabolised by CYP2C9. The effects of CYP2C9 inducers such as rifampicin on the pharmacokinetic of irbesartan have not been evaluated. The pharmacokinetic of digoxin was not altered by co-administration of irbesartan.

Additional information on hydrochlorothiazide interactions: when administered concurrently, the following medicinal products may interact with thiazide diuretics:

*Alcohol:* potentiation of orthostatic hypotension may occur;

*Antidiabetic medicinal products (oral agents and insulins):* dosage adjustment of the antidiabetic medicinal product may be required (see section 4.4);

*Colestyramine and Colestipol resins:* absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins;

*Corticosteroids, ACTH:* electrolyte depletion, particularly hypokalaemia, may be increased;

*Digitalis glycosides:* thiazide induced hypokalaemia or hypomagnaesemia favour the onset of digitalis-induced cardiac arrhythmias (see section 4.4);

*Non-steroidal anti-inflammatory drugs:* the administration of a non-steroidal anti-inflammatory drug may reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics in some patients;

*Pressor amines (e.g. noradrenaline):* the effect of pressor amines may be decreased, but not sufficiently to preclude their use;

*Nondepolarizing skeletal muscle relaxants (e.g. tubocurarine):* the effect of nondepolarizing skeletal muscle relaxants may be potentiated by hydrochlorothiazide;

*Antigout medicinal products:* dosage adjustments of antigout medicinal products may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol;

*Calcium salts:* thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements or calcium sparing medicinal products (e.g. vitamin D therapy) must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly;

*Other interactions:* the hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides. Anticholinergic agents (e.g. atropine, beperiden) may increase the bioavailability of thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate. Thiazides may increase the risk of adverse effects caused by amantadine. Thiazides may reduce the renal excretion of cytotoxic medicinal products (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.



### 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).

Thiazides cross the placental barrier and appear in cord blood. They may cause a decrease in placental perfusion, foetal electrolyte disturbances and possibly other reactions that have occurred in the adults. Cases of neonatal thrombocytopenia, or foetal or neonatal jaundice have been reported with maternal thiazide therapy. Since Irbesartan Hydrochlorothiazide BMS contains hydrochlorothiazide, it is not recommended during the first trimester of pregnancy. A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy.



Lactation:

Because no information is available regarding the use of Irbesartan Hydrochlorothiazide BMS during breast-feeding, Irbesartan Hydrochlorothiazide 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 Hydrochlorothiazide BMS is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur during treatment of hypertension.

### 4.8 Undesirable effects

Irbesartan/hydrochlorothiazide combination:
Table 1 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled trials in which 898 hypertensive patients received various doses (range: 37.5 mg/6.25 mg to 300 mg/25 mg irbesartan/hydrochlorothiazide).

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

**Table 1:** Adverse Reactions in Placebo-Controlled Trials and Spontaneous Reports*

| | | |
|---|---|---|
| *Investigations:* | Common: | increases in blood urea nitrogen (BUN), creatinine and creatine kinase |
| | Uncommon: | decreases in serum potassium and sodium |
| *Cardiac disorders:* | Uncommon: | syncope, hypotension, tachycardia, oedema |
| *Nervous system disorders:* | Common: | dizziness |
| | Uncommon: | orthostatic dizziness |

| | | |
|---|---|---|
| | Not known: | headache |
| *Ear and labyrinth disorders:* | Not known: | tinnitus |
| *Respiratory, thoracic and mediastinal disorders:* | Not known: | cough |
| *Gastrointestinal disorders:* | Common:<br>Uncommon:<br>Not known: | nausea/vomiting<br>diarrhoea<br>dyspepsia, dysgeusia |
| *Renal and urinary disorders:* | Common:<br>Not known: | abnormal urination<br>impaired renal function including isolated cases of renal failure in patients at risk (see section 4.4) |
| *Musculoskeletal and connective tissue disorders:* | Uncommon:<br>Not known: | swelling extremity<br>arthralgia, myalgia |
| *Metabolism and nutrition disorders:* | Not known: | hyperkalaemia |
| *Vascular disorders:* | Uncommon: | flushing |
| *General disorders and administration site conditions:* | Common: | fatigue |
| *Immune system disorders:* | Not known: | cases of hypersensitivity reactions such as angioedema, rash, urticaria |
| *Hepatobiliary disorders:* | Not known: | hepatitis, abnormal liver function |
| *Reproductive system and breast disorders:* | Uncommon: | sexual dysfunction, libido changes |

* Frequency for adverse reactions detected by spontaneous reports is described as "not known"

Additional information on individual components: in addition to the adverse reactions listed above for the combination product, other adverse reactions previously reported with one of the individual components may be potential adverse reactions with Irbesartan Hydrochlorothiazide BMS. Tables 2 and 3 below detail the adverse reactions reported with the individual components of Irbesartan Hydrochlorothiazide BMS.

**Table 2:** Adverse reactions reported with the use of **irbesartan** alone

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

**Table 3:** Adverse reactions (regardless of relationship to medicinal product) reported with the use of **hydrochlorothiazide** alone

| | | |
|---|---|---|
| *Investigations:* | Not known: | electrolyte imbalance (including hypokalaemia and hyponatraemia, see section 4.4), hyperuricaemia, glycosuria, hyperglycaemia, increases in cholesterol and triglycerides |
| *Cardiac disorders:* | Not known: | cardiac arrhythmias |
| *Blood and lymphatic system disorders:* | Not known: | aplastic anaemia, bone marrow depression, neutropenia/agranulocytosis, haemolytic anaemia, leucopenia, thrombocytopenia |
| *Nervous system disorders:* | Not known: | vertigo, paraesthesia, light-headedness, restlessness |
| *Eye disorders:* | Not known: | transient blurred vision, xanthopsia |
| *Respiratory, thoracic and mediastinal disorders:* | Not known: | respiratory distress (including pneumonitis and pulmonary oedema) |
| *Gastrointestinal disorders:* | Not known: | pancreatitis, anorexia, diarrhoea, constipation, gastric irritation, sialadenitis, loss of appetite |
| *Renal and urinary disorders:* | Not known: | interstitial nephritis, renal dysfunction |

| | | |
|---|---|---|
| *Skin and subcutaneous tissue disorders:* | Not known: | anaphylactic reactions, toxic epidermal necrolysis, necrotizing angitis (vasculitis, cutaneous vasculitis), cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, photosensitivity reactions, rash, urticaria |
| *Musculoskeletal and connective tissue disorders:* | Not known: | weakness, muscle spasm |
| *Vascular disorders:* | Not known: | postural hypotension |
| *General disorders and administration site conditions:* | Not known: | fever |
| *Hepatobiliary disorders:* | Not known: | jaundice (intrahepatic cholestatic jaundice) |
| *Psychiatric disorders:* | Not known: | depression, sleep disturbances |

The dose dependent adverse events of hydrochlorothiazide (particularly electrolyte disturbances) may increase when titrating the hydrochlorothiazide.

### 4.9 Overdose

No specific information is available on the treatment of overdose with Irbesartan Hydrochlorothiazide BMS. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and/or gastric lavage. Activated charcoal may be useful in the treatment of overdose. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacements given quickly.

The most likely manifestations of irbesartan overdose are expected to be hypotension and tachycardia; bradycardia might also occur.

Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloremia, hyponatraemia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasms and/or accentuate cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic medicinal products.

Irbesartan is not removed by haemodialysis. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.



## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: angiotensin-II antagonists, combinations
ATC code: C09DA04.

Irbesartan Hydrochlorothiazide BMS is a combination of an angiotensin-II receptor antagonist, irbesartan, and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Irbesartan is a potent, orally active, selective angiotensin-II receptor ($AT_1$ subtype) 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 in patients without risk of electrolyte imbalance (see sections 4.4 and 4.5). 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.

Hydrochlorothiazide is a thiazide diuretic. The mechanism of antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity, increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. Presumably through blockade of the renin-angiotensin-aldosterone system, co-administration of irbesartan tends to reverse the potassium loss associated with these diuretics. With hydrochlorothiazide, onset of diuresis occurs in 2 hours, and peak effect occurs at about 4 hours, while the action persists for approximately 6-12 hours.

The combination of hydrochlorothiazide and irbesartan produces dose-related additive reductions in blood pressure across their therapeutic dose ranges. The addition of 12.5 mg hydrochlorothiazide to 300 mg irbesartan once daily in patients not adequately controlled on 300 mg irbesartan alone resulted in further placebo-corrected diastolic blood pressure reductions at trough (24 hours post-dosing) of 6.1 mm Hg. The combination of 300 mg irbesartan and 12.5 mg hydrochlorothiazide resulted in an overall placebo-subtracted systolic/diastolic reductions of up to 13.6/11.5 mm Hg.

Limited clinical data (7 out of 22 patients) suggest that patients not controlled with the 300 mg/12.5 mg combination may respond when uptitrated to 300 mg/25 mg. In these patients, an incremental blood pressure lowering effect was observed for both systolic blood pressure (SBP) and diastolic blood pressure (DBP) (13.3 and 8.3 mm Hg, respectively).

Once daily dosing with 150 mg irbesartan and 12.5 mg hydrochlorothiazide gave systolic/diastolic mean placebo-adjusted blood pressure reductions at trough (24 hours post-dosing) of 12.9/6.9 mm Hg in patients with mild-to-moderate hypertension. Peak effects occurred at 3-6 hours. When assessed by ambulatory blood pressure monitoring, the combination 150 mg irbesartan and 12.5 mg hydrochlorothiazide once daily produced consistent reduction in blood pressure over the 24 hours period with mean 24-hour placebo-subtracted systolic/diastolic reductions of 15.8/10.0 mm Hg. When measured by ambulatory blood pressure monitoring, the trough to peak effects of Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg were 100%. The trough to peak effects measured by cuff during office visits were 68% and 76% for Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg and Irbesartan Hydrochlorothiazide BMS 300 mg/12.5 mg, respectively. These 24-hour effects were observed without excessive blood pressure lowering at peak and are consistent with safe and effective blood-pressure lowering over the once-daily dosing interval.



In patients not adequately controlled on 25 mg hydrochlorothiazide alone, the addition of irbesartan gave an added placebo-subtracted systolic/diastolic mean reduction of 11.1/7.2 mm Hg.

The blood pressure lowering effect of irbesartan in combination with hydrochlorothiazide is apparent after the first dose and substantially present within 1-2 weeks, with the maximal effect occurring by 6-8 weeks. In long-term follow-up studies, the effect of irbesartan/hydrochlorothiazide was maintained for over one year. Although not specifically studied with the Irbesartan Hydrochlorothiazide BMS, rebound hypertension has not been seen with either irbesartan or hydrochlorothiazide.

The effect of the combination of irbesartan and hydrochlorothiazide on morbidity and mortality has not been studied. Epidemiological studies have shown that long term treatment with hydrochlorothiazide reduces the risk of cardiovascular mortality and morbidity.

There is no difference in response to Irbesartan Hydrochlorothiazide BMS, regardless of 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 non-black patients.

Efficacy and safety of Irbesartan Hydrochlorothiazide BMS as initial therapy for severe hypertension (defined as SeDBP ≥ 110 mmHg) was evaluated in a multicenter, randomized, double-blind, active-controlled, 8-week, parallel-arm study. A total of 697 patients were randomized in a 2:1 ratio to either irbesartan/hydrochlorothiazide 150 mg/12.5 mg or to irbesartan 150 mg and systematically force-titrated (before assessing the response to the lower dose) after one week to irbesartan/hydrochlorothiazide 300 mg/25 mg or irbesartan 300 mg, respectively.

The study recruited 58% males. The mean age of patients was 52.5 years, 13% were ≥ 65 years of age, and just 2% were ≥ 75 years of age. Twelve percent (12%) of patients were diabetic, 34% were hyperlipidemic and the most frequent cardiovascular condition was stable angina pectoris in 3.5% of the participants.

The primary objective of this study was to compare the proportion of patients whose SeDBP was controlled (SeDBP < 90 mmHg) at Week 5 of treatment. Forty-seven percent (47.2%) of patients on the combination achieved trough SeDBP < 90 mmHg compared to 33.2% of patients on irbesartan ($p = 0.0005$). The mean baseline blood pressure was approximately 172/113 mmHg in each treatment group and decreases of SeSBP/SeDBP at five weeks were 30.8/24.0 mmHg and 21.1/19.3 mmHg for irbesartan/hydrochlorothiazide and irbesartan, respectively ($p < 0.0001$).

The types and incidences of adverse events reported for patients treated with the combination were similar to the adverse event profile for patients on monotherapy. During the 8-week treatment period, there were no reported cases of syncope in either treatment group. There were 0.6% and 0% of patients with hypotension and 2.8% and 3.1% of patients with dizziness as adverse reactions reported in the combination and monotherapy groups, respectively.



## 5.2 Pharmacokinetic properties

Concomitant administration of hydrochlorothiazide and irbesartan has no effect on the pharmacokinetics of either medicinal product.

Irbesartan and hydrochlorothiazide are orally active agents and do not require biotransformation for their activity. Following oral administration of Irbesartan Hydrochlorothiazide BMS, the absolute oral bioavailability is 60-80% and 50-80% for irbesartan and hydrochlorothiazide, respectively. Food does not affect the bioavailability of Irbesartan Hydrochlorothiazide BMS. Peak plasma concentration occurs at 1.5-2 hours after oral administration for irbesartan and 1-2.5 hours for hydrochlorothiazide.

Plasma protein binding of irbesartan is approximately 96%, with negligible binding to cellular blood components. The volume of distribution for irbesartan is 53-93 litres. Hydrochlorothiazide is 68% protein-bound in the plasma, and its apparent volume of distribution is 0.83-1.14 l/kg.

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 was observed; the mechanism for this is unknown. The total body and renal clearance are 157-176 and 3.0-3.5 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. The mean plasma half-life of hydrochlorothiazide reportedly ranges from 5-15 hours.

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 and its metabolites are eliminated by both biliary and renal pathways. After either oral or intravenous 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. Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidneys. At least 61% of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier, and is excreted in breast milk.

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. In patients with creatinine clearance < 20 ml/min, the elimination half-life of hydrochlorothiazide was reported to increase to 21 hours.

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

Irbesartan/hydrochlorothiazide: the potential toxicity of the irbesartan/hydrochlorothiazide combination after oral administration was evaluated in rats and macaques in studies lasting up to 6 months. There were no toxicological findings observed of relevance to human therapeutic use. The following changes, observed in rats and macaques receiving the irbesartan/hydrochlorothiazide combination at 10/10 and 90/90 mg/kg/day, were also seen with one of the two medicinal products alone and/or were secondary to decreases in blood pressure (no significant toxicologic interactions were observed):

- kidney changes, characterized by slight increases in serum urea and creatinine, and hyperplasia/hypertrophy of the juxtaglomerular apparatus, which are a direct consequence of the interaction of irbesartan with the renin-angiotensin system;
- slight decreases in erythrocyte parameters (erythrocytes, haemoglobin, haematocrit);
- stomach discoloration, ulcers and focal necrosis of gastric mucosa were observed in few rats in a 6 months toxicity study at irbesartan 90 mg/kg/day, hydrochlorothiazide 90 mg/kg/day, and irbesartan/hydrochlorothiazide 10/10 mg/kg/day. These lesions were not observed in macaques;
- decreases in serum potassium due to hydrochlorothiazide and partly prevented when hydrochlorothiazide was given in combination with irbesartan.

Most of the above mentioned effects appear to be due to the pharmacological activity of irbesartan (blockade of angiotensin-II-induced inhibition of renin release, with stimulation of the renin-producing cells) and occur also with angiotensin converting enzyme inhibitors. These findings appear to have no relevance to the use of therapeutic doses of irbesartan/hydrochlorothiazide in humans.

No teratogenic effects were seen in rats given irbesartan and hydrochlorothiazide in combination at doses that produced maternal toxicity. The effects of the irbesartan/hydrochlorothiazide combination on fertility have not been evaluated in animal studies, as there is no evidence of adverse effect on fertility in animals or humans with either irbesartan or hydrochlorothiazide when administered alone. However, another angiotensin-II antagonist affected fertility parameters in animal studies when given alone. These findings were also observed with lower doses of this other angiotensin-II antagonist when given in combination with hydrochlorothiazide.

There was no evidence of mutagenicity or clastogenicity with the irbesartan/hydrochlorothiazide combination. The carcinogenic potential of irbesartan and hydrochlorothiazide in combination has not been evaluated in animal studies.

Irbesartan: 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 kidneys (such as interstitial nephritis, tubular distention, 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 was noted at doses causing significant maternal toxicity, including mortality. No teratogenic effects were observed in the rat or rabbit.

Hydrochlorothiazide: although equivocal evidence for a genotoxic or carcinogenic effect was found in some experimental models, the extensive human experience with hydrochlorothiazide has failed to show an association between its use and an increase in neoplasms.



## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Microcrystalline cellulose
Croscarmellose sodium
Lactose monohydrate
Magnesium stearate
Colloidal hydrated silica
Pregelatinised maize starch
Red and yellow ferric oxides (E172)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from moisture.

### 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 tablets; 7 blister cards of 8 x 1 tablets 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/1/06/369/006-010

## 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 Hydrochlorothiazide BMS 150 mg/12.5 mg film-coated tablets.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg of irbesartan and 12.5 mg of hydrochlorothiazide.

Excipient:
Each film-coated tablet contains 38.5 mg of lactose (as lactose monohydrate).

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.
Peach, biconvex, oval-shaped, with a heart debossed on one side and the number 2875 engraved on the other side.



## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment of essential hypertension.
This fixed dose combination is indicated in adult patients whose blood pressure is not adequately controlled on irbesartan or hydrochlorothiazide alone (see section 5.1).

### 4.2 Posology and method of administration

Irbesartan Hydrochlorothiazide BMS can be taken once daily, with or without food.
Dose titration with the individual components (i.e. irbesartan and hydrochlorothiazide) may be recommended.

When clinically appropriate, direct change from monotherapy to the fixed combinations may be considered:

- Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg may be administered in patients whose blood pressure is not adequately controlled with hydrochlorothiazide or irbesartan 150 mg alone;
- Irbesartan Hydrochlorothiazide BMS 300 mg/12.5 mg may be administered in patients insufficiently controlled by irbesartan 300 mg or by Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg.
- Irbesartan Hydrochlorothiazide BMS 300 mg/25 mg may be administered in patients insufficiently controlled by Irbesartan Hydrochlorothiazide BMS 300 mg/12.5 mg.

Doses higher than 300 mg irbesartan/25 mg hydrochlorothiazide once daily are not recommended.
When necessary, Irbesartan Hydrochlorothiazide BMS may be administered with another antihypertensive medicinal product (see section 4.5).

Renal impairment: due to the hydrochlorothiazide component, Irbesartan Hydrochlorothiazide BMS is not recommended for patients with severe renal dysfunction (creatinine clearance < 30 ml/min). Loop diuretics are preferred to thiazides in this population. No dosage adjustment is necessary in patients with renal impairment whose renal creatinine clearance is ≥ 30 ml/min (see sections 4.3 and 4.4).

Hepatic impairment: Irbesartan Hydrochlorothiazide BMS is not indicated in patients with severe hepatic impairment. Thiazides should be used with caution in patients with impaired hepatic function. No dosage adjustment of Irbesartan Hydrochlorothiazide BMS is necessary in patients with mild to moderate hepatic impairment (see section 4.3).

Elderly patients: no dosage adjustment of Irbesartan Hydrochlorothiazide BMS is necessary in elderly patients.

Paediatric patients: Irbesartan Hydrochlorothiazide BMS is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

## 4.3 Contraindications

- Hypersensitivity to the active substances, to any of the excipients (see section 6.1), or to other sulfonamide-derived substances (hydrochlorothiazide is a sulfonamide-derived substance)
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)
- Severe renal impairment (creatinine clearance < 30 ml/min)
- Refractory hypokalaemia, hypercalcaemia
- Severe hepatic impairment, biliary cirrhosis and cholestasis

## 4.4 Special warnings and precautions for use

Hypotension - Volume-depleted patients: Irbesartan Hydrochlorothiazide BMS has been rarely associated with symptomatic hypotension in hypertensive patients without other risk factors for hypotension. Symptomatic hypotension may be expected to 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 initiating therapy with Irbesartan Hydrochlorothiazide BMS.

Renal artery stenosis - 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 angiotensin converting enzyme inhibitors or angiotensin-II receptor antagonists. While this is not documented with Irbesartan Hydrochlorothiazide BMS, a similar effect should be anticipated.

Renal impairment and kidney transplantation: when Irbesartan Hydrochlorothiazide BMS is used in patients with impaired renal function, a periodic monitoring of potassium, creatinine and uric acid serum levels is recommended. There is no experience regarding the administration of Irbesartan Hydrochlorothiazide BMS in patients with a recent kidney transplantation. Irbesartan Hydrochlorothiazide BMS should not be used in patients with severe renal impairment (creatinine clearance < 30 ml/min) (see section 4.3). Thiazide diuretic-associated azotemia may occur in patients with impaired renal function. No dosage adjustment is necessary in patients with renal impairment whose creatinine clearance is ≥ 30 ml/min. However, in patients with mild to moderate renal impairment (creatinine clearance ≥ 30 ml/min but < 60 ml/min) this fixed dose combination should be administered with caution.

Hepatic impairment: thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. There is no clinical experience with Irbesartan Hydrochlorothiazide BMS in patients with hepatic impairment.

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 Hydrochlorothiazide BMS is not recommended.

Metabolic and endocrine effects: thiazide therapy may impair glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Latent diabetes mellitus may become manifest during thiazide therapy.
Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy; however at the 12.5 mg dose contained in Irbesartan Hydrochlorothiazide BMS, minimal or no effects were reported.
Hyperuricaemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Electrolyte imbalance: as for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.
Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloremic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting.
Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with irbesartan may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH. Conversely, due to the irbesartan component of Irbesartan Hydrochlorothiazide BMS hyperkalaemia might occur, especially in the presence of renal impairment and/or heart failure, and diabetes mellitus. Adequate monitoring of serum potassium in patients at risk is recommended. Potassium-sparing diuretics, potassium supplements or potassium-containing salts substitutes should be co-administered cautiously with Irbesartan Hydrochlorothiazide BMS (see section 4.5).
There is no evidence that irbesartan would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.
Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.
Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnaesemia.

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

Anti-doping test: hydrochlorothiazide contained in this medicinal product could produce a positive analytic result in an anti-doping test.

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, azotemia, oliguria, or rarely acute renal failure. As with any antihypertensive agent, excessive blood pressure decrease in patients with ischemic cardiopathy or ischemic cardiovascular disease could result in a myocardial infarction or stroke.
Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.
Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics.
Cases of photosensitivity reactions have been reported with thiazides diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

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.

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

Other antihypertensive agents: the antihypertensive effect of Irbesartan Hydrochlorothiazide BMS may be increased with the concomitant use of other antihypertensive agents. Irbesartan and hydrochlorothiazide (at doses up to 300 mg irbesartan/25 mg hydrochlorothiazide) have been safely administered with other antihypertensive agents including calcium channel blockers and beta-adrenergic blockers. Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with irbesartan with or without thiazide diuretics unless the volume depletion is corrected first (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. Furthermore, renal clearance of lithium is reduced by thiazides so the risk of lithium toxicity could be increased with Irbesartan Hydrochlorothiazide BMS. Therefore, the combination of lithium and Irbesartan Hydrochlorothiazide BMS is not recommended (see section 4.4). If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Medicinal products affecting potassium: the potassium-depleting effect of hydrochlorothiazide is attenuated by the potassium-sparing effect of irbesartan. However, this effect of hydrochlorothiazide on serum potassium would be expected to be potentiated by other medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, penicillin G sodium). Conversely, based on the experience with the use of other medicinal products that blunt 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 sodium) may lead to increases in serum potassium. Adequate monitoring of serum potassium in patients at risk is recommended (see section 4.4).



Medicinal products affected by serum potassium disturbances: periodic monitoring of serum potassium is recommended when Irbesartan Hydrochlorothiazide BMS is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics).

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

Additional information on irbesartan interactions: in clinical studies, the pharmacokinetic of irbesartan is not affected by hydrochlorothiazide. Irbesartan is mainly metabolised by CYP2C9 and to a lesser

extent by glucuronidation. No significant pharmacokinetic or pharmacodynamic interactions were observed when irbesartan was coadministered with warfarin, a medicinal product metabolised by CYP2C9. The effects of CYP2C9 inducers such as rifampicin on the pharmacokinetic of irbesartan have not been evaluated. The pharmacokinetic of digoxin was not altered by co-administration of irbesartan.

Additional information on hydrochlorothiazide interactions: when administered concurrently, the following medicinal products may interact with thiazide diuretics:

*Alcohol:* potentiation of orthostatic hypotension may occur;

*Antidiabetic medicinal products (oral agents and insulins):* dosage adjustment of the antidiabetic medicinal product may be required (see section 4.4);

*Colestyramine and Colestipol resins:* absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins;

*Corticosteroids, ACTH:* electrolyte depletion, particularly hypokalaemia, may be increased;

*Digitalis glycosides:* thiazide induced hypokalaemia or hypomagnaesemia favour the onset of digitalis-induced cardiac arrhythmias (see section 4.4);

*Non-steroidal anti-inflammatory drugs:* the administration of a non-steroidal anti-inflammatory drug may reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics in some patients;

*Pressor amines (e.g. noradrenaline):* the effect of pressor amines may be decreased, but not sufficiently to preclude their use;

*Nondepolarizing skeletal muscle relaxants (e.g. tubocurarine):* the effect of nondepolarizing skeletal muscle relaxants may be potentiated by hydrochlorothiazide;

*Antigout medicinal products:* dosage adjustments of antigout medicinal products may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol;

*Calcium salts:* thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements or calcium sparing medicinal products (e.g. vitamin D therapy) must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly;

*Other interactions:* the hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides. Anticholinergic agents (e.g. atropine, beperiden) may increase the bioavailability of thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate. Thiazides may increase the risk of adverse effects caused by amantadine. Thiazides may reduce the renal excretion of cytotoxic medicinal products (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.



## 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).

Thiazides cross the placental barrier and appear in cord blood. They may cause a decrease in placental perfusion, foetal electrolyte disturbances and possibly other reactions that have occurred in the adults. Cases of neonatal thrombocytopenia, or foetal or neonatal jaundice have been reported with maternal thiazide therapy. Since Irbesartan Hydrochlorothiazide BMS contains hydrochlorothiazide, it is not recommended during the first trimester of pregnancy. A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy.



Lactation:

Because no information is available regarding the use of Irbesartan Hydrochlorothiazide BMS during breast-feeding, Irbesartan Hydrochlorothiazide 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 Hydrochlorothiazide BMS is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur during treatment of hypertension.

### 4.8 Undesirable effects

Irbesartan/hydrochlorothiazide combination:
Table 1 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled trials in which 898 hypertensive patients received various doses (range: 37.5 mg/6.25 mg to 300 mg/25 mg irbesartan/hydrochlorothiazide).

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

**Table 1:** Adverse Reactions in Placebo-Controlled Trials and Spontaneous Reports*

| | | |
|---|---|---|
| *Investigations:* | Common: | increases in blood urea nitrogen (BUN), creatinine and creatine kinase |
| | Uncommon: | decreases in serum potassium and sodium |
| *Cardiac disorders:* | Uncommon: | syncope, hypotension, tachycardia, oedema |
| *Nervous system disorders:* | Common: | dizziness |
| | Uncommon: | orthostatic dizziness |
| | Not known: | headache |

| | | |
|---|---|---|
| *Ear and labyrinth disorders:* | Not known: | tinnitus |
| *Respiratory, thoracic and mediastinal disorders:* | Not known: | cough |
| *Gastrointestinal disorders:* | Common:<br>Uncommon:<br>Not known: | nausea/vomiting<br>diarrhoea<br>dyspepsia, dysgeusia |
| *Renal and urinary disorders:* | Common:<br>Not known: | abnormal urination<br>impaired renal function including isolated cases of renal failure in patients at risk (see section 4.4) |
| *Musculoskeletal and connective tissue disorders:* | Uncommon:<br>Not known: | swelling extremity<br>arthralgia, myalgia |
| *Metabolism and nutrition disorders:* | Not known: | hyperkalaemia |
| *Vascular disorders:* | Uncommon: | flushing |
| *General disorders and administration site conditions:* | Common: | fatigue |
| *Immune system disorders:* | Not known: | cases of hypersensitivity reactions such as angioedema, rash, urticaria |
| *Hepatobiliary disorders:* | Not known: | hepatitis, abnormal liver function |
| *Reproductive system and breast disorders:* | Uncommon: | sexual dysfunction, libido changes |

* Frequency for adverse reactions detected by spontaneous reports is described as "not known"

Additional information on individual components: in addition to the adverse reactions listed above for the combination product, other adverse reactions previously reported with one of the individual components may be potential adverse reactions with Irbesartan Hydrochlorothiazide BMS. Tables 2 and 3 below detail the adverse reactions reported with the individual components of Irbesartan Hydrochlorothiazide BMS.



**Table 2:** Adverse reactions reported with the use of **irbesartan** alone

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

**Table 3:** Adverse reactions (regardless of relationship to medicinal product) reported with the use of **hydrochlorothiazide** alone

| | | |
|---|---|---|
| *Investigations:* | Not known: | electrolyte imbalance (including hypokalaemia and hyponatraemia, see section 4.4), hyperuricaemia, glycosuria, hyperglycaemia, increases in cholesterol and triglycerides |
| *Cardiac disorders:* | Not known: | cardiac arrhythmias |
| *Blood and lymphatic system disorders:* | Not known: | aplastic anaemia, bone marrow depression, neutropenia/agranulocytosis, haemolytic anaemia, leucopenia, thrombocytopenia |
| *Nervous system disorders:* | Not known: | vertigo, paraesthesia, light-headedness, restlessness |
| *Eye disorders:* | Not known: | transient blurred vision, xanthopsia |
| *Respiratory, thoracic and mediastinal disorders:* | Not known: | respiratory distress (including pneumonitis and pulmonary oedema) |
| *Gastrointestinal disorders:* | Not known: | pancreatitis, anorexia, diarrhoea, constipation, gastric irritation, sialadenitis, loss of appetite |
| *Renal and urinary disorders:* | Not known: | interstitial nephritis, renal dysfunction |
| *Skin and subcutaneous tissue disorders:* | Not known: | anaphylactic reactions, toxic epidermal necrolysis, necrotizing angitis (vasculitis, cutaneous vasculitis), cutaneous lupus erythematosus-like reactions, reactivation of |

| | | |
|---|---|---|
| | | cutaneous lupus erythematosus, photosensitivity reactions, rash, urticaria |
| *Musculoskeletal and connective tissue disorders:* | Not known: | weakness, muscle spasm |
| *Vascular disorders:* | Not known: | postural hypotension |
| *General disorders and administration site conditions:* | Not known: | fever |
| *Hepatobiliary disorders:* | Not known: | jaundice (intrahepatic cholestatic jaundice) |
| *Psychiatric disorders:* | Not known: | depression, sleep disturbances |

The dose dependent adverse events of hydrochlorothiazide (particularly electrolyte disturbances) may increase when titrating the hydrochlorothiazide.

### 4.9 Overdose

No specific information is available on the treatment of overdose with Irbesartan Hydrochlorothiazide BMS. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and/or gastric lavage. Activated charcoal may be useful in the treatment of overdose. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacements given quickly.

The most likely manifestations of irbesartan overdose are expected to be hypotension and tachycardia; bradycardia might also occur.

Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloremia, hyponatraemia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasms and/or accentuate cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic medicinal products.

Irbesartan is not removed by haemodialysis. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.



## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: angiotensin-II antagonists, combinations
ATC code: C09DA04.

Irbesartan Hydrochlorothiazide BMS is a combination of an angiotensin-II receptor antagonist, irbesartan, and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Irbesartan is a potent, orally active, selective angiotensin-II receptor ($AT_1$ subtype) 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 in patients without risk of electrolyte imbalance (see sections 4.4 and 4.5). 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.

Hydrochlorothiazide is a thiazide diuretic. The mechanism of antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity, increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. Presumably through blockade of the renin-angiotensin-aldosterone system, co-administration of irbesartan tends to reverse the potassium loss associated with these diuretics. With hydrochlorothiazide, onset of diuresis occurs in 2 hours, and peak effect occurs at about 4 hours, while the action persists for approximately 6-12 hours.

The combination of hydrochlorothiazide and irbesartan produces dose-related additive reductions in blood pressure across their therapeutic dose ranges. The addition of 12.5 mg hydrochlorothiazide to 300 mg irbesartan once daily in patients not adequately controlled on 300 mg irbesartan alone resulted in further placebo-corrected diastolic blood pressure reductions at trough (24 hours post-dosing) of 6.1 mm Hg. The combination of 300 mg irbesartan and 12.5 mg hydrochlorothiazide resulted in an overall placebo-subtracted systolic/diastolic reductions of up to 13.6/11.5 mm Hg.

Limited clinical data (7 out of 22 patients) suggest that patients not controlled with the 300 mg/12.5 mg combination may respond when uptitrated to 300 mg/25 mg. In these patients, an incremental blood pressure lowering effect was observed for both systolic blood pressure (SBP) and diastolic blood pressure (DBP) (13.3 and 8.3 mm Hg, respectively).

Once daily dosing with 150 mg irbesartan and 12.5 mg hydrochlorothiazide gave systolic/diastolic mean placebo-adjusted blood pressure reductions at trough (24 hours post-dosing) of 12.9/6.9 mm Hg in patients with mild-to-moderate hypertension. Peak effects occurred at 3-6 hours. When assessed by ambulatory blood pressure monitoring, the combination 150 mg irbesartan and 12.5 mg hydrochlorothiazide once daily produced consistent reduction in blood pressure over the 24 hours period with mean 24-hour placebo-subtracted systolic/diastolic reductions of 15.8/10.0 mm Hg. When measured by ambulatory blood pressure monitoring, the trough to peak effects of Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg were 100%. The trough to peak effects measured by cuff during office visits were 68% and 76% for Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg and Irbesartan Hydrochlorothiazide BMS 300 mg/12.5 mg, respectively. These 24-hour effects were observed without excessive blood pressure lowering at peak and are consistent with safe and effective blood-pressure lowering over the once-daily dosing interval.

In patients not adequately controlled on 25 mg hydrochlorothiazide alone, the addition of irbesartan gave an added placebo-subtracted systolic/diastolic mean reduction of 11.1/7.2 mm Hg.

The blood pressure lowering effect of irbesartan in combination with hydrochlorothiazide is apparent after the first dose and substantially present within 1-2 weeks, with the maximal effect occurring by 6-8 weeks. In long-term follow-up studies, the effect of irbesartan/hydrochlorothiazide was maintained for over one year. Although not specifically studied with the Irbesartan Hydrochlorothiazide BMS, rebound hypertension has not been seen with either irbesartan or hydrochlorothiazide.

The effect of the combination of irbesartan and hydrochlorothiazide on morbidity and mortality has not been studied. Epidemiological studies have shown that long term treatment with hydrochlorothiazide reduces the risk of cardiovascular mortality and morbidity.

There is no difference in response to Irbesartan Hydrochlorothiazide BMS, regardless of 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 non-black patients.

Efficacy and safety of Irbesartan Hydrochlorothiazide BMS as initial therapy for severe hypertension (defined as SeDBP ≥ 110 mmHg) was evaluated in a multicenter, randomized, double-blind, active-

controlled, 8-week, parallel-arm study. A total of 697 patients were randomized in a 2:1 ratio to either irbesartan/hydrochlorothiazide 150 mg/12.5 mg or to irbesartan 150 mg and systematically force-titrated (before assessing the response to the lower dose) after one week to irbesartan/hydrochlorothiazide 300 mg/25 mg or irbesartan 300 mg, respectively.

The study recruited 58% males. The mean age of patients was 52.5 years, 13% were ≥ 65 years of age, and just 2% were ≥ 75 years of age. Twelve percent (12%) of patients were diabetic, 34% were hyperlipidemic and the most frequent cardiovascular condition was stable angina pectoris in 3.5% of the participants.

The primary objective of this study was to compare the proportion of patients whose SeDBP was controlled (SeDBP < 90 mmHg) at Week 5 of treatment. Forty-seven percent (47.2%) of patients on the combination achieved trough SeDBP < 90 mmHg compared to 33.2% of patients on irbesartan (p = 0.0005). The mean baseline blood pressure was approximately 172/113 mmHg in each treatment group and decreases of SeSBP/SeDBP at five weeks were 30.8/24.0 mmHg and 21.1/19.3 mmHg for irbesartan/hydrochlorothiazide and irbesartan, respectively (p < 0.0001).

The types and incidences of adverse events reported for patients treated with the combination were similar to the adverse event profile for patients on monotherapy. During the 8-week treatment period, there were no reported cases of syncope in either treatment group. There were 0.6% and 0% of patients with hypotension and 2.8% and 3.1% of patients with dizziness as adverse reactions reported in the combination and monotherapy groups, respectively.



## 5.2 Pharmacokinetic properties

Concomitant administration of hydrochlorothiazide and irbesartan has no effect on the pharmacokinetics of either medicinal product.

Irbesartan and hydrochlorothiazide are orally active agents and do not require biotransformation for their activity. Following oral administration of Irbesartan Hydrochlorothiazide BMS, the absolute oral bioavailability is 60-80% and 50-80% for irbesartan and hydrochlorothiazide, respectively. Food does not affect the bioavailability of Irbesartan Hydrochlorothiazide BMS. Peak plasma concentration occurs at 1.5-2 hours after oral administration for irbesartan and 1-2.5 hours for hydrochlorothiazide.

Plasma protein binding of irbesartan is approximately 96%, with negligible binding to cellular blood components. The volume of distribution for irbesartan is 53-93 litres. Hydrochlorothiazide is 68% protein-bound in the plasma, and its apparent volume of distribution is 0.83-1.14 l/kg.

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 was observed; the mechanism for this is unknown. The total body and renal clearance are 157-176 and 3.0-3.5 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. The mean plasma half-life of hydrochlorothiazide reportedly ranges from 5-15 hours.

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 and its metabolites are eliminated by both biliary and renal pathways. After either oral or intravenous

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. Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidneys. At least 61% of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier, and is excreted in breast milk.

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. In patients with creatinine clearance < 20 ml/min, the elimination half-life of hydrochlorothiazide was reported to increase to 21 hours.

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

Irbesartan/hydrochlorothiazide: the potential toxicity of the irbesartan/hydrochlorothiazide combination after oral administration was evaluated in rats and macaques in studies lasting up to 6 months. There were no toxicological findings observed of relevance to human therapeutic use. The following changes, observed in rats and macaques receiving the irbesartan/hydrochlorothiazide combination at 10/10 and 90/90 mg/kg/day, were also seen with one of the two medicinal products alone and/or were secondary to decreases in blood pressure (no significant toxicologic interactions were observed):

- kidney changes, characterized by slight increases in serum urea and creatinine, and hyperplasia/hypertrophy of the juxtaglomerular apparatus, which are a direct consequence of the interaction of irbesartan with the renin-angiotensin system;
- slight decreases in erythrocyte parameters (erythrocytes, haemoglobin, haematocrit);
- stomach discoloration, ulcers and focal necrosis of gastric mucosa were observed in few rats in a 6 months toxicity study at irbesartan 90 mg/kg/day, hydrochlorothiazide 90 mg/kg/day, and irbesartan/hydrochlorothiazide 10/10 mg/kg/day. These lesions were not observed in macaques;
- decreases in serum potassium due to hydrochlorothiazide and partly prevented when hydrochlorothiazide was given in combination with irbesartan.

Most of the above mentioned effects appear to be due to the pharmacological activity of irbesartan (blockade of angiotensin-II-induced inhibition of renin release, with stimulation of the renin-producing cells) and occur also with angiotensin converting enzyme inhibitors. These findings appear to have no relevance to the use of therapeutic doses of irbesartan/hydrochlorothiazide in humans.



No teratogenic effects were seen in rats given irbesartan and hydrochlorothiazide in combination at doses that produced maternal toxicity. The effects of the irbesartan/hydrochlorothiazide combination on fertility have not been evaluated in animal studies, as there is no evidence of adverse effect on fertility in animals or humans with either irbesartan or hydrochlorothiazide when administered alone. However, another angiotensin-II antagonist affected fertility parameters in animal studies when given alone. These findings were also observed with lower doses of this other angiotensin-II antagonist when given in combination with hydrochlorothiazide.

There was no evidence of mutagenicity or clastogenicity with the irbesartan/hydrochlorothiazide combination. The carcinogenic potential of irbesartan and hydrochlorothiazide in combination has not been evaluated in animal studies.

Irbesartan: 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 kidneys (such as interstitial nephritis, tubular distention, 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 was noted at doses causing significant maternal toxicity, including mortality. No teratogenic effects were observed in the rat or rabbit.

Hydrochlorothiazide: although equivocal evidence for a genotoxic or carcinogenic effect was found in some experimental models, the extensive human experience with hydrochlorothiazide has failed to show an association between its use and an increase in neoplasms.

## 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
Red and yellow ferric oxides
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.
Store in the original package in order to protect from moisture.

### 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 tablets; 7 blister cards of 8 x 1 film-coated tablets 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/1/06/369/011-016

## 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 Hydrochlorothiazide BMS 300 mg/12.5 mg film-coated tablets.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg of irbesartan and 12.5 mg of hydrochlorothiazide.

Excipient:
Each film-coated tablet contains 89.5 mg of lactose (as lactose monohydrate).

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.
Peach, biconvex, oval-shaped, with a heart debossed on one side and the number 2876 engraved on the other side.



## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment of essential hypertension.
This fixed dose combination is indicated in adult patients whose blood pressure is not adequately controlled on irbesartan or hydrochlorothiazide alone (see section 5.1).

### 4.2 Posology and method of administration

Irbesartan Hydrochlorothiazide BMS can be taken once daily, with or without food.
Dose titration with the individual components (i.e. irbesartan and hydrochlorothiazide) may be recommended.

When clinically appropriate, direct change from monotherapy to the fixed combinations may be considered:

- Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg may be administered in patients whose blood pressure is not adequately controlled with hydrochlorothiazide or irbesartan 150 mg alone;
- Irbesartan Hydrochlorothiazide BMS 300 mg/12.5 mg may be administered in patients insufficiently controlled by irbesartan 300 mg or by Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg.
- Irbesartan Hydrochlorothiazide BMS 300 mg/25 mg may be administered in patients insufficiently controlled by Irbesartan Hydrochlorothiazide BMS 300 mg/12.5 mg.

Doses higher than 300 mg irbesartan/25 mg hydrochlorothiazide once daily are not recommended.
When necessary, Irbesartan Hydrochlorothiazide BMS may be administered with another antihypertensive medicinal product (see section 4.5).

Renal impairment: due to the hydrochlorothiazide component, Irbesartan Hydrochlorothiazide BMS is not recommended for patients with severe renal dysfunction (creatinine clearance < 30 ml/min). Loop diuretics are preferred to thiazides in this population. No dosage adjustment is necessary in patients with renal impairment whose renal creatinine clearance is ≥ 30 ml/min (see sections 4.3 and 4.4).

Hepatic impairment: Irbesartan Hydrochlorothiazide BMS is not indicated in patients with severe hepatic impairment. Thiazides should be used with caution in patients with impaired hepatic function. No dosage adjustment of Irbesartan Hydrochlorothiazide BMS is necessary in patients with mild to moderate hepatic impairment (see section 4.3).

Elderly patients: no dosage adjustment of Irbesartan Hydrochlorothiazide BMS is necessary in elderly patients.

Paediatric patients: Irbesartan Hydrochlorothiazide BMS is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

## 4.3 Contraindications

- Hypersensitivity to the active substances, to any of the excipients (see section 6.1), or to other sulfonamide-derived substances (hydrochlorothiazide is a sulfonamide-derived substance)
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)
- Severe renal impairment (creatinine clearance < 30 ml/min)
- Refractory hypokalaemia, hypercalcaemia
- Severe hepatic impairment, biliary cirrhosis and cholestasis

## 4.4 Special warnings and precautions for use

Hypotension - Volume-depleted patients: Irbesartan Hydrochlorothiazide BMS has been rarely associated with symptomatic hypotension in hypertensive patients without other risk factors for hypotension. Symptomatic hypotension may be expected to 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 initiating therapy with Irbesartan Hydrochlorothiazide BMS.

Renal artery stenosis - 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 angiotensin converting enzyme inhibitors or angiotensin-II receptor antagonists. While this is not documented with Irbesartan Hydrochlorothiazide BMS, a similar effect should be anticipated.

Renal impairment and kidney transplantation: when Irbesartan Hydrochlorothiazide BMS is used in patients with impaired renal function, a periodic monitoring of potassium, creatinine and uric acid serum levels is recommended. There is no experience regarding the administration of Irbesartan Hydrochlorothiazide BMS in patients with a recent kidney transplantation. Irbesartan Hydrochlorothiazide BMS should not be used in patients with severe renal impairment (creatinine clearance < 30 ml/min) (see section 4.3). Thiazide diuretic-associated azotemia may occur in patients with impaired renal function. No dosage adjustment is necessary in patients with renal impairment whose creatinine clearance is ≥ 30 ml/min. However, in patients with mild to moderate renal impairment (creatinine clearance ≥ 30 ml/min but < 60 ml/min) this fixed dose combination should be administered with caution.

Hepatic impairment: thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. There is no clinical experience with Irbesartan Hydrochlorothiazide BMS in patients with hepatic impairment.

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 Hydrochlorothiazide BMS is not recommended.

Metabolic and endocrine effects: thiazide therapy may impair glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Latent diabetes mellitus may become manifest during thiazide therapy.
Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy; however at the 12.5 mg dose contained in Irbesartan Hydrochlorothiazide BMS, minimal or no effects were reported.
Hyperuricaemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Electrolyte imbalance: as for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.
Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloremic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting.
Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with irbesartan may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH. Conversely, due to the irbesartan component of Irbesartan Hydrochlorothiazide BMS hyperkalaemia might occur, especially in the presence of renal impairment and/or heart failure, and diabetes mellitus. Adequate monitoring of serum potassium in patients at risk is recommended. Potassium-sparing diuretics, potassium supplements or potassium-containing salts substitutes should be co-administered cautiously with Irbesartan Hydrochlorothiazide BMS (see section 4.5).
There is no evidence that irbesartan would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.
Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.
Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnaesemia.

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

Anti-doping test: hydrochlorothiazide contained in this medicinal product could produce a positive analytic result in an anti-doping test.

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, azotemia, oliguria, or rarely acute renal failure. As with any antihypertensive agent, excessive blood pressure decrease in patients with ischemic cardiopathy or ischemic cardiovascular disease could result in a myocardial infarction or stroke.
Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.
Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics.
Cases of photosensitivity reactions have been reported with thiazides diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

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.

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

Other antihypertensive agents: the antihypertensive effect of Irbesartan Hydrochlorothiazide BMS may be increased with the concomitant use of other antihypertensive agents. Irbesartan and hydrochlorothiazide (at doses up to 300 mg irbesartan/25 mg hydrochlorothiazide) have been safely administered with other antihypertensive agents including calcium channel blockers and beta-adrenergic blockers. Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with irbesartan with or without thiazide diuretics unless the volume depletion is corrected first (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. Furthermore, renal clearance of lithium is reduced by thiazides so the risk of lithium toxicity could be increased with Irbesartan Hydrochlorothiazide BMS. Therefore, the combination of lithium and Irbesartan Hydrochlorothiazide BMS is not recommended (see section 4.4). If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Medicinal products affecting potassium: the potassium-depleting effect of hydrochlorothiazide is attenuated by the potassium-sparing effect of irbesartan. However, this effect of hydrochlorothiazide on serum potassium would be expected to be potentiated by other medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, penicillin G sodium). Conversely, based on the experience with the use of other medicinal products that blunt 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 sodium) may lead to increases in serum potassium. Adequate monitoring of serum potassium in patients at risk is recommended (see section 4.4).



Medicinal products affected by serum potassium disturbances: periodic monitoring of serum potassium is recommended when Irbesartan Hydrochlorothiazide BMS is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics).

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

Additional information on irbesartan interactions: in clinical studies, the pharmacokinetic of irbesartan is not affected by hydrochlorothiazide. Irbesartan is mainly metabolised by CYP2C9 and to a lesser

extent by glucuronidation. No significant pharmacokinetic or pharmacodynamic interactions were observed when irbesartan was coadministered with warfarin, a medicinal product metabolised by CYP2C9. The effects of CYP2C9 inducers such as rifampicin on the pharmacokinetic of irbesartan have not been evaluated. The pharmacokinetic of digoxin was not altered by co-administration of irbesartan.

Additional information on hydrochlorothiazide interactions: when administered concurrently, the following medicinal products may interact with thiazide diuretics:

*Alcohol:* potentiation of orthostatic hypotension may occur;

*Antidiabetic medicinal products (oral agents and insulins):* dosage adjustment of the antidiabetic medicinal product may be required (see section 4.4);

*Colestyramine and Colestipol resins:* absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins;

*Corticosteroids, ACTH:* electrolyte depletion, particularly hypokalaemia, may be increased;

*Digitalis glycosides:* thiazide induced hypokalaemia or hypomagnaesemia favour the onset of digitalis-induced cardiac arrhythmias (see section 4.4);

*Non-steroidal anti-inflammatory drugs:* the administration of a non-steroidal anti-inflammatory drug may reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics in some patients;

*Pressor amines (e.g. noradrenaline):* the effect of pressor amines may be decreased, but not sufficiently to preclude their use;

*Nondepolarizing skeletal muscle relaxants (e.g. tubocurarine):* the effect of nondepolarizing skeletal muscle relaxants may be potentiated by hydrochlorothiazide;

*Antigout medicinal products:* dosage adjustments of antigout medicinal products may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol;

*Calcium salts:* thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements or calcium sparing medicinal products (e.g. vitamin D therapy) must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly;

*Other interactions:* the hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides. Anticholinergic agents (e.g. atropine, beperiden) may increase the bioavailability of thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate. Thiazides may increase the risk of adverse effects caused by amantadine. Thiazides may reduce the renal excretion of cytotoxic medicinal products (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.



### 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).

Thiazides cross the placental barrier and appear in cord blood. They may cause a decrease in placental perfusion, foetal electrolyte disturbances and possibly other reactions that have occurred in the adults. Cases of neonatal thrombocytopenia, or foetal or neonatal jaundice have been reported with maternal thiazide therapy. Since Irbesartan Hydrochlorothiazide BMS contains hydrochlorothiazide, it is not recommended during the first trimester of pregnancy. A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy.



Lactation:

Because no information is available regarding the use of Irbesartan Hydrochlorothiazide BMS during breast-feeding, Irbesartan Hydrochlorothiazide 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 Hydrochlorothiazide BMS is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur during treatment of hypertension.

### 4.8 Undesirable effects

Irbesartan/hydrochlorothiazide combination:
Table 1 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled trials in which 898 hypertensive patients received various doses (range: 37.5 mg/6.25 mg to 300 mg/25 mg irbesartan/hydrochlorothiazide).

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

**Table 1:** Adverse Reactions in Placebo-Controlled Trials and Spontaneous Reports*

| | | |
|---|---|---|
| *Investigations:* | Common: | increases in blood urea nitrogen (BUN), creatinine and creatine kinase |
| | Uncommon: | decreases in serum potassium and sodium |
| *Cardiac disorders:* | Uncommon: | syncope, hypotension, tachycardia, oedema |
| *Nervous system disorders:* | Common: | dizziness |
| | Uncommon: | orthostatic dizziness |
| | Not known: | headache |

| | | |
|---|---|---|
| *Ear and labyrinth disorders:* | Not known: | tinnitus |
| *Respiratory, thoracic and mediastinal disorders:* | Not known: | cough |
| *Gastrointestinal disorders:* | Common:<br>Uncommon:<br>Not known: | nausea/vomiting<br>diarrhoea<br>dyspepsia, dysgeusia |
| *Renal and urinary disorders:* | Common:<br>Not known: | abnormal urination<br>impaired renal function including isolated cases of renal failure in patients at risk (see section 4.4) |
| *Musculoskeletal and connective tissue disorders:* | Uncommon:<br>Not known: | swelling extremity<br>arthralgia, myalgia |
| *Metabolism and nutrition disorders:* | Not known: | hyperkalaemia |
| *Vascular disorders:* | Uncommon: | flushing |
| *General disorders and administration site conditions:* | Common: | fatigue |
| *Immune system disorders:* | Not known: | cases of hypersensitivity reactions such as angioedema, rash, urticaria |
| *Hepatobiliary disorders:* | Not known: | hepatitis, abnormal liver function |
| *Reproductive system and breast disorders:* | Uncommon: | sexual dysfunction, libido changes |

* Frequency for adverse reactions detected by spontaneous reports is described as "not known"

Additional information on individual components: in addition to the adverse reactions listed above for the combination product, other adverse reactions previously reported with one of the individual components may be potential adverse reactions with Irbesartan Hydrochlorothiazide BMS. Tables 2 and 3 below detail the adverse reactions reported with the individual components of Irbesartan Hydrochlorothiazide BMS.



**Table 2:** Adverse reactions reported with the use of **irbesartan** alone

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

**Table 3:** Adverse reactions (regardless of relationship to medicinal product) reported with the use of **hydrochlorothiazide** alone

| | | |
|---|---|---|
| *Investigations:* | Not known: | electrolyte imbalance (including hypokalaemia and hyponatraemia, see section 4.4), hyperuricaemia, glycosuria, hyperglycaemia, increases in cholesterol and triglycerides |
| *Cardiac disorders:* | Not known: | cardiac arrhythmias |
| *Blood and lymphatic system disorders:* | Not known: | aplastic anaemia, bone marrow depression, neutropenia/agranulocytosis, haemolytic anaemia, leucopenia, thrombocytopenia |
| *Nervous system disorders:* | Not known: | vertigo, paraesthesia, light-headedness, restlessness |
| *Eye disorders:* | Not known: | transient blurred vision, xanthopsia |
| *Respiratory, thoracic and mediastinal disorders:* | Not known: | respiratory distress (including pneumonitis and pulmonary oedema) |
| *Gastrointestinal disorders:* | Not known: | pancreatitis, anorexia, diarrhoea, constipation, gastric irritation, sialadenitis, loss of appetite |
| *Renal and urinary disorders:* | Not known: | interstitial nephritis, renal dysfunction |
| *Skin and subcutaneous tissue disorders:* | Not known: | anaphylactic reactions, toxic epidermal necrolysis, necrotizing angitis (vasculitis, cutaneous vasculitis), cutaneous lupus erythematosus-like reactions, reactivation of |

| | | |
|---|---|---|
| | | cutaneous lupus erythematosus, photosensitivity reactions, rash, urticaria |
| *Musculoskeletal and connective tissue disorders:* | Not known: | weakness, muscle spasm |
| *Vascular disorders:* | Not known: | postural hypotension |
| *General disorders and administration site conditions:* | Not known: | fever |
| *Hepatobiliary disorders:* | Not known: | jaundice (intrahepatic cholestatic jaundice) |
| *Psychiatric disorders:* | Not known: | depression, sleep disturbances |

The dose dependent adverse events of hydrochlorothiazide (particularly electrolyte disturbances) may increase when titrating the hydrochlorothiazide.

### 4.9 Overdose

No specific information is available on the treatment of overdose with Irbesartan Hydrochlorothiazide BMS. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and/or gastric lavage. Activated charcoal may be useful in the treatment of overdose. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacements given quickly.

The most likely manifestations of irbesartan overdose are expected to be hypotension and tachycardia; bradycardia might also occur.

Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloremia, hyponatraemia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasms and/or accentuate cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic medicinal products.

Irbesartan is not removed by haemodialysis. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.



## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: angiotensin-II antagonists, combinations
ATC code: C09DA04.

Irbesartan Hydrochlorothiazide BMS is a combination of an angiotensin-II receptor antagonist, irbesartan, and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Irbesartan is a potent, orally active, selective angiotensin-II receptor ($AT_1$ subtype) 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 in patients without risk of electrolyte imbalance (see sections 4.4 and 4.5). 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.

Hydrochlorothiazide is a thiazide diuretic. The mechanism of antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity, increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. Presumably through blockade of the renin-angiotensin-aldosterone system, co-administration of irbesartan tends to reverse the potassium loss associated with these diuretics. With hydrochlorothiazide, onset of diuresis occurs in 2 hours, and peak effect occurs at about 4 hours, while the action persists for approximately 6-12 hours.

The combination of hydrochlorothiazide and irbesartan produces dose-related additive reductions in blood pressure across their therapeutic dose ranges. The addition of 12.5 mg hydrochlorothiazide to 300 mg irbesartan once daily in patients not adequately controlled on 300 mg irbesartan alone resulted in further placebo-corrected diastolic blood pressure reductions at trough (24 hours post-dosing) of 6.1 mm Hg. The combination of 300 mg irbesartan and 12.5 mg hydrochlorothiazide resulted in an overall placebo-subtracted systolic/diastolic reductions of up to 13.6/11.5 mm Hg.

Limited clinical data (7 out of 22 patients) suggest that patients not controlled with the 300 mg/12.5 mg combination may respond when uptitrated to 300 mg/25 mg. In these patients, an incremental blood pressure lowering effect was observed for both systolic blood pressure (SBP) and diastolic blood pressure (DBP) (13.3 and 8.3 mm Hg, respectively).

Once daily dosing with 150 mg irbesartan and 12.5 mg hydrochlorothiazide gave systolic/diastolic mean placebo-adjusted blood pressure reductions at trough (24 hours post-dosing) of 12.9/6.9 mm Hg in patients with mild-to-moderate hypertension. Peak effects occurred at 3-6 hours. When assessed by ambulatory blood pressure monitoring, the combination 150 mg irbesartan and 12.5 mg hydrochlorothiazide once daily produced consistent reduction in blood pressure over the 24 hours period with mean 24-hour placebo-subtracted systolic/diastolic reductions of 15.8/10.0 mm Hg. When measured by ambulatory blood pressure monitoring, the trough to peak effects of Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg were 100%. The trough to peak effects measured by cuff during office visits were 68% and 76% for Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg and Irbesartan Hydrochlorothiazide BMS 300 mg/12.5 mg, respectively. These 24-hour effects were observed without excessive blood pressure lowering at peak and are consistent with safe and effective blood-pressure lowering over the once-daily dosing interval.

In patients not adequately controlled on 25 mg hydrochlorothiazide alone, the addition of irbesartan gave an added placebo-subtracted systolic/diastolic mean reduction of 11.1/7.2 mm Hg.

The blood pressure lowering effect of irbesartan in combination with hydrochlorothiazide is apparent after the first dose and substantially present within 1-2 weeks, with the maximal effect occurring by 6-8 weeks. In long-term follow-up studies, the effect of irbesartan/hydrochlorothiazide was maintained for over one year. Although not specifically studied with the Irbesartan Hydrochlorothiazide BMS, rebound hypertension has not been seen with either irbesartan or hydrochlorothiazide.

The effect of the combination of irbesartan and hydrochlorothiazide on morbidity and mortality has not been studied. Epidemiological studies have shown that long term treatment with hydrochlorothiazide reduces the risk of cardiovascular mortality and morbidity.

There is no difference in response to Irbesartan Hydrochlorothiazide BMS, regardless of 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 non-black patients.

Efficacy and safety of Irbesartan Hydrochlorothiazide BMS as initial therapy for severe hypertension (defined as SeDBP ≥ 110 mmHg) was evaluated in a multicenter, randomized, double-blind, active-

controlled, 8-week, parallel-arm study. A total of 697 patients were randomized in a 2:1 ratio to either irbesartan/hydrochlorothiazide 150 mg/12.5 mg or to irbesartan 150 mg and systematically force-titrated (before assessing the response to the lower dose) after one week to irbesartan/hydrochlorothiazide 300 mg/25 mg or irbesartan 300 mg, respectively.

The study recruited 58% males. The mean age of patients was 52.5 years, 13% were ≥ 65 years of age, and just 2% were ≥ 75 years of age. Twelve percent (12%) of patients were diabetic, 34% were hyperlipidemic and the most frequent cardiovascular condition was stable angina pectoris in 3.5% of the participants.

The primary objective of this study was to compare the proportion of patients whose SeDBP was controlled (SeDBP < 90 mmHg) at Week 5 of treatment. Forty-seven percent (47.2%) of patients on the combination achieved trough SeDBP < 90 mmHg compared to 33.2% of patients on irbesartan ($p = 0.0005$). The mean baseline blood pressure was approximately 172/113 mmHg in each treatment group and decreases of SeSBP/SeDBP at five weeks were 30.8/24.0 mmHg and 21.1/19.3 mmHg for irbesartan/hydrochlorothiazide and irbesartan, respectively ($p < 0.0001$).

The types and incidences of adverse events reported for patients treated with the combination were similar to the adverse event profile for patients on monotherapy. During the 8-week treatment period, there were no reported cases of syncope in either treatment group. There were 0.6% and 0% of patients with hypotension and 2.8% and 3.1% of patients with dizziness as adverse reactions reported in the combination and monotherapy groups, respectively.



## 5.2 Pharmacokinetic properties

Concomitant administration of hydrochlorothiazide and irbesartan has no effect on the pharmacokinetics of either medicinal product.

Irbesartan and hydrochlorothiazide are orally active agents and do not require biotransformation for their activity. Following oral administration of Irbesartan Hydrochlorothiazide BMS, the absolute oral bioavailability is 60-80% and 50-80% for irbesartan and hydrochlorothiazide, respectively. Food does not affect the bioavailability of Irbesartan Hydrochlorothiazide BMS. Peak plasma concentration occurs at 1.5-2 hours after oral administration for irbesartan and 1-2.5 hours for hydrochlorothiazide.

Plasma protein binding of irbesartan is approximately 96%, with negligible binding to cellular blood components. The volume of distribution for irbesartan is 53-93 litres. Hydrochlorothiazide is 68% protein-bound in the plasma, and its apparent volume of distribution is 0.83-1.14 l/kg.

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 was observed; the mechanism for this is unknown. The total body and renal clearance are 157-176 and 3.0-3.5 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. The mean plasma half-life of hydrochlorothiazide reportedly ranges from 5-15 hours.

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 and its metabolites are eliminated by both biliary and renal pathways. After either oral or intravenous

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. Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidneys. At least 61% of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier, and is excreted in breast milk.

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. In patients with creatinine clearance < 20 ml/min, the elimination half-life of hydrochlorothiazide was reported to increase to 21 hours.

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

Irbesartan/hydrochlorothiazide: the potential toxicity of the irbesartan/hydrochlorothiazide combination after oral administration was evaluated in rats and macaques in studies lasting up to 6 months. There were no toxicological findings observed of relevance to human therapeutic use. The following changes, observed in rats and macaques receiving the irbesartan/hydrochlorothiazide combination at 10/10 and 90/90 mg/kg/day, were also seen with one of the two medicinal products alone and/or were secondary to decreases in blood pressure (no significant toxicologic interactions were observed):

- kidney changes, characterized by slight increases in serum urea and creatinine, and hyperplasia/hypertrophy of the juxtaglomerular apparatus, which are a direct consequence of the interaction of irbesartan with the renin-angiotensin system;
- slight decreases in erythrocyte parameters (erythrocytes, haemoglobin, haematocrit);
- stomach discoloration, ulcers and focal necrosis of gastric mucosa were observed in few rats in a 6 months toxicity study at irbesartan 90 mg/kg/day, hydrochlorothiazide 90 mg/kg/day, and irbesartan/hydrochlorothiazide 10/10 mg/kg/day. These lesions were not observed in macaques;
- decreases in serum potassium due to hydrochlorothiazide and partly prevented when hydrochlorothiazide was given in combination with irbesartan.

Most of the above mentioned effects appear to be due to the pharmacological activity of irbesartan (blockade of angiotensin-II-induced inhibition of renin release, with stimulation of the renin-producing cells) and occur also with angiotensin converting enzyme inhibitors. These findings appear to have no relevance to the use of therapeutic doses of irbesartan/hydrochlorothiazide in humans.



No teratogenic effects were seen in rats given irbesartan and hydrochlorothiazide in combination at doses that produced maternal toxicity. The effects of the irbesartan/hydrochlorothiazide combination on fertility have not been evaluated in animal studies, as there is no evidence of adverse effect on fertility in animals or humans with either irbesartan or hydrochlorothiazide when administered alone. However, another angiotensin-II antagonist affected fertility parameters in animal studies when given alone. These findings were also observed with lower doses of this other angiotensin-II antagonist when given in combination with hydrochlorothiazide.

There was no evidence of mutagenicity or clastogenicity with the irbesartan/hydrochlorothiazide combination. The carcinogenic potential of irbesartan and hydrochlorothiazide in combination has not been evaluated in animal studies.

Irbesartan: 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 kidneys (such as interstitial nephritis, tubular distention, 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 was noted at doses causing significant maternal toxicity, including mortality. No teratogenic effects were observed in the rat or rabbit.

Hydrochlorothiazide: although equivocal evidence for a genotoxic or carcinogenic effect was found in some experimental models, the extensive human experience with hydrochlorothiazide has failed to show an association between its use and an increase in neoplasms.

## 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
Red and yellow ferric oxides
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.
Store in the original package in order to protect from moisture.

### 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 tablets; 7 blister cards of 8 x 1 film-coated tablets 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/1/06/369/017-022

## 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 Hydrochlorothiazide BMS 300 mg/25 mg film-coated tablets.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg of irbesartan and 25 mg of hydrochlorothiazide.

Excipient:
Each film-coated tablet contains 53.3 mg of lactose (as lactose monohydrate).

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.
Pink, biconvex, oval-shaped, with a heart debossed on one side and the number 2788 engraved on the other side.



## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment of essential hypertension.
This fixed dose combination is indicated in adult patients whose blood pressure is not adequately controlled on irbesartan or hydrochlorothiazide alone (see section 5.1).

### 4.2 Posology and method of administration

Irbesartan Hydrochlorothiazide BMS can be taken once daily, with or without food.
Dose titration with the individual components (i.e. irbesartan and hydrochlorothiazide) may be recommended.

When clinically appropriate, direct change from monotherapy to the fixed combinations may be considered:

- Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg may be administered in patients whose blood pressure is not adequately controlled with hydrochlorothiazide or irbesartan 150 mg alone;
- Irbesartan Hydrochlorothiazide BMS 300 mg/12.5 mg may be administered in patients insufficiently controlled by irbesartan 300 mg or by Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg.
- Irbesartan Hydrochlorothiazide BMS 300 mg/25 mg may be administered in patients insufficiently controlled by Irbesartan Hydrochlorothiazide BMS 300 mg/12.5 mg.

Doses higher than 300 mg irbesartan/25 mg hydrochlorothiazide once daily are not recommended.
When necessary, Irbesartan Hydrochlorothiazide BMS may be administered with another antihypertensive medicinal product (see section 4.5).

Renal impairment: due to the hydrochlorothiazide component, Irbesartan Hydrochlorothiazide BMS is not recommended for patients with severe renal dysfunction (creatinine clearance < 30 ml/min). Loop diuretics are preferred to thiazides in this population. No dosage adjustment is necessary in patients with renal impairment whose renal creatinine clearance is ≥ 30 ml/min (see sections 4.3 and 4.4).

Hepatic impairment: Irbesartan Hydrochlorothiazide BMS is not indicated in patients with severe hepatic impairment. Thiazides should be used with caution in patients with impaired hepatic function. No dosage adjustment of Irbesartan Hydrochlorothiazide BMS is necessary in patients with mild to moderate hepatic impairment (see section 4.3).

Elderly patients: no dosage adjustment of Irbesartan Hydrochlorothiazide BMS is necessary in elderly patients.

Paediatric patients: Irbesartan Hydrochlorothiazide BMS is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

## 4.3 Contraindications

- Hypersensitivity to the active substances, to any of the excipients (see section 6.1), or to other sulfonamide-derived substances (hydrochlorothiazide is a sulfonamide-derived substance)
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)
- Severe renal impairment (creatinine clearance < 30 ml/min)
- Refractory hypokalaemia, hypercalcaemia
- Severe hepatic impairment, biliary cirrhosis and cholestasis

## 4.4 Special warnings and precautions for use

Hypotension - Volume-depleted patients: Irbesartan Hydrochlorothiazide BMS has been rarely associated with symptomatic hypotension in hypertensive patients without other risk factors for hypotension. Symptomatic hypotension may be expected to 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 initiating therapy with Irbesartan Hydrochlorothiazide BMS.

Renal artery stenosis - 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 angiotensin converting enzyme inhibitors or angiotensin-II receptor antagonists. While this is not documented with Irbesartan Hydrochlorothiazide BMS, a similar effect should be anticipated.

Renal impairment and kidney transplantation: when Irbesartan Hydrochlorothiazide BMS is used in patients with impaired renal function, a periodic monitoring of potassium, creatinine and uric acid serum levels is recommended. There is no experience regarding the administration of Irbesartan Hydrochlorothiazide BMS in patients with a recent kidney transplantation. Irbesartan Hydrochlorothiazide BMS should not be used in patients with severe renal impairment (creatinine clearance < 30 ml/min) (see section 4.3). Thiazide diuretic-associated azotemia may occur in patients with impaired renal function. No dosage adjustment is necessary in patients with renal impairment whose creatinine clearance is ≥ 30 ml/min. However, in patients with mild to moderate renal impairment (creatinine clearance ≥ 30 ml/min but < 60 ml/min) this fixed dose combination should be administered with caution.

Hepatic impairment: thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. There is no clinical experience with Irbesartan Hydrochlorothiazide BMS in patients with hepatic impairment.

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 Hydrochlorothiazide BMS is not recommended.

Metabolic and endocrine effects: thiazide therapy may impair glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Latent diabetes mellitus may become manifest during thiazide therapy.
Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy; however at the 12.5 mg dose contained in Irbesartan Hydrochlorothiazide BMS, minimal or no effects were reported.
Hyperuricaemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Electrolyte imbalance: as for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.
Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloremic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting.
Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with irbesartan may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH. Conversely, due to the irbesartan component of Irbesartan Hydrochlorothiazide BMS hyperkalaemia might occur, especially in the presence of renal impairment and/or heart failure, and diabetes mellitus. Adequate monitoring of serum potassium in patients at risk is recommended. Potassium-sparing diuretics, potassium supplements or potassium-containing salts substitutes should be co-administered cautiously with Irbesartan Hydrochlorothiazide BMS (see section 4.5).
There is no evidence that irbesartan would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.
Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.
Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnaesemia.

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

Anti-doping test: hydrochlorothiazide contained in this medicinal product could produce a positive analytic result in an anti-doping test.

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, azotemia, oliguria, or rarely acute renal failure. As with any antihypertensive agent, excessive blood pressure decrease in patients with ischemic cardiopathy or ischemic cardiovascular disease could result in a myocardial infarction or stroke.
Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.
Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics.
Cases of photosensitivity reactions have been reported with thiazides diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

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.

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

Other antihypertensive agents: the antihypertensive effect of Irbesartan Hydrochlorothiazide BMS may be increased with the concomitant use of other antihypertensive agents. Irbesartan and hydrochlorothiazide (at doses up to 300 mg irbesartan/25 mg hydrochlorothiazide) have been safely administered with other antihypertensive agents including calcium channel blockers and beta-adrenergic blockers. Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with irbesartan with or without thiazide diuretics unless the volume depletion is corrected first (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. Furthermore, renal clearance of lithium is reduced by thiazides so the risk of lithium toxicity could be increased with Irbesartan Hydrochlorothiazide BMS. Therefore, the combination of lithium and Irbesartan Hydrochlorothiazide BMS is not recommended (see section 4.4). If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Medicinal products affecting potassium: the potassium-depleting effect of hydrochlorothiazide is attenuated by the potassium-sparing effect of irbesartan. However, this effect of hydrochlorothiazide on serum potassium would be expected to be potentiated by other medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, penicillin G sodium). Conversely, based on the experience with the use of other medicinal products that blunt 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 sodium) may lead to increases in serum potassium. Adequate monitoring of serum potassium in patients at risk is recommended (see section 4.4).



Medicinal products affected by serum potassium disturbances: periodic monitoring of serum potassium is recommended when Irbesartan Hydrochlorothiazide BMS is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics).

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

Additional information on irbesartan interactions: in clinical studies, the pharmacokinetic of irbesartan is not affected by hydrochlorothiazide. Irbesartan is mainly metabolised by CYP2C9 and to a lesser

extent by glucuronidation. No significant pharmacokinetic or pharmacodynamic interactions were observed when irbesartan was coadministered with warfarin, a medicinal product metabolised by CYP2C9. The effects of CYP2C9 inducers such as rifampicin on the pharmacokinetic of irbesartan have not been evaluated. The pharmacokinetic of digoxin was not altered by co-administration of irbesartan.

Additional information on hydrochlorothiazide interactions: when administered concurrently, the following medicinal products may interact with thiazide diuretics:

*Alcohol:* potentiation of orthostatic hypotension may occur;

*Antidiabetic medicinal products (oral agents and insulins):* dosage adjustment of the antidiabetic medicinal product may be required (see section 4.4);

*Colestyramine and Colestipol resins:* absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins;

*Corticosteroids, ACTH:* electrolyte depletion, particularly hypokalaemia, may be increased;

*Digitalis glycosides:* thiazide induced hypokalaemia or hypomagnaesemia favour the onset of digitalis-induced cardiac arrhythmias (see section 4.4);

*Non-steroidal anti-inflammatory drugs:* the administration of a non-steroidal anti-inflammatory drug may reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics in some patients;

*Pressor amines (e.g. noradrenaline):* the effect of pressor amines may be decreased, but not sufficiently to preclude their use;

*Nondepolarizing skeletal muscle relaxants (e.g. tubocurarine):* the effect of nondepolarizing skeletal muscle relaxants may be potentiated by hydrochlorothiazide;

*Antigout medicinal products:* dosage adjustments of antigout medicinal products may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol;

*Calcium salts:* thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements or calcium sparing medicinal products (e.g. vitamin D therapy) must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly;

*Other interactions:* the hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides. Anticholinergic agents (e.g. atropine, beperiden) may increase the bioavailability of thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate. Thiazides may increase the risk of adverse effects caused by amantadine. Thiazides may reduce the renal excretion of cytotoxic medicinal products (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.



### 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).

Thiazides cross the placental barrier and appear in cord blood. They may cause a decrease in placental perfusion, foetal electrolyte disturbances and possibly other reactions that have occurred in the adults. Cases of neonatal thrombocytopenia, or foetal or neonatal jaundice have been reported with maternal thiazide therapy. Since Irbesartan Hydrochlorothiazide BMS contains hydrochlorothiazide, it is not recommended during the first trimester of pregnancy. A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy.



Lactation:

Because no information is available regarding the use of Irbesartan Hydrochlorothiazide BMS during breast-feeding, Irbesartan Hydrochlorothiazide 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 Hydrochlorothiazide BMS is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur during treatment of hypertension.

### 4.8 Undesirable effects

Irbesartan/hydrochlorothiazide combination:
Table 1 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled trials in which 898 hypertensive patients received various doses (range: 37.5 mg/6.25 mg to 300 mg/25 mg irbesartan/hydrochlorothiazide).

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

**Table 1:** Adverse Reactions in Placebo-Controlled Trials and Spontaneous Reports*

| | | |
|---|---|---|
| *Investigations:* | Common: | increases in blood urea nitrogen (BUN), creatinine and creatine kinase |
| | Uncommon: | decreases in serum potassium and sodium |
| *Cardiac disorders:* | Uncommon: | syncope, hypotension, tachycardia, oedema |
| *Nervous system disorders:* | Common: | dizziness |
| | Uncommon: | orthostatic dizziness |
| | Not known: | headache |

| | | |
|---|---|---|
| *Ear and labyrinth disorders:* | Not known: | tinnitus |
| *Respiratory, thoracic and mediastinal disorders:* | Not known: | cough |
| *Gastrointestinal disorders:* | Common:<br>Uncommon:<br>Not known: | nausea/vomiting<br>diarrhoea<br>dyspepsia, dysgeusia |
| *Renal and urinary disorders:* | Common:<br>Not known: | abnormal urination<br>impaired renal function including isolated cases of renal failure in patients at risk (see section 4.4) |
| *Musculoskeletal and connective tissue disorders:* | Uncommon:<br>Not known: | swelling extremity<br>arthralgia, myalgia |
| *Metabolism and nutrition disorders:* | Not known: | hyperkalaemia |
| *Vascular disorders:* | Uncommon: | flushing |
| *General disorders and administration site conditions:* | Common: | fatigue |
| *Immune system disorders:* | Not known: | cases of hypersensitivity reactions such as angioedema, rash, urticaria |
| *Hepatobiliary disorders:* | Not known: | hepatitis, abnormal liver function |
| *Reproductive system and breast disorders:* | Uncommon: | sexual dysfunction, libido changes |

* Frequency for adverse reactions detected by spontaneous reports is described as "not known"

Additional information on individual components: in addition to the adverse reactions listed above for the combination product, other adverse reactions previously reported with one of the individual components may be potential adverse reactions with Irbesartan Hydrochlorothiazide BMS. Tables 2 and 3 below detail the adverse reactions reported with the individual components of Irbesartan Hydrochlorothiazide BMS.

**Table 2:** Adverse reactions reported with the use of **irbesartan** alone

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

**Table 3:** Adverse reactions (regardless of relationship to medicinal product) reported with the use of **hydrochlorothiazide** alone

| | | |
|---|---|---|
| *Investigations:* | Not known: | electrolyte imbalance (including hypokalaemia and hyponatraemia, see section 4.4), hyperuricaemia, glycosuria, hyperglycaemia, increases in cholesterol and triglycerides |
| *Cardiac disorders:* | Not known: | cardiac arrhythmias |
| *Blood and lymphatic system disorders:* | Not known: | aplastic anaemia, bone marrow depression, neutropenia/agranulocytosis, haemolytic anaemia, leucopenia, thrombocytopenia |
| *Nervous system disorders:* | Not known: | vertigo, paraesthesia, light-headedness, restlessness |
| *Eye disorders:* | Not known: | transient blurred vision, xanthopsia |
| *Respiratory, thoracic and mediastinal disorders:* | Not known: | respiratory distress (including pneumonitis and pulmonary oedema) |
| *Gastrointestinal disorders:* | Not known: | pancreatitis, anorexia, diarrhoea, constipation, gastric irritation, sialadenitis, loss of appetite |
| *Renal and urinary disorders:* | Not known: | interstitial nephritis, renal dysfunction |
| *Skin and subcutaneous tissue disorders:* | Not known: | anaphylactic reactions, toxic epidermal necrolysis, necrotizing angitis (vasculitis, cutaneous vasculitis), cutaneous lupus erythematosus-like reactions, reactivation of |

| | | |
|---|---|---|
| | | cutaneous lupus erythematosus, photosensitivity reactions, rash, urticaria |
| *Musculoskeletal and connective tissue disorders:* | Not known: | weakness, muscle spasm |
| *Vascular disorders:* | Not known: | postural hypotension |
| *General disorders and administration site conditions:* | Not known: | fever |
| *Hepatobiliary disorders:* | Not known: | jaundice (intrahepatic cholestatic jaundice) |
| *Psychiatric disorders:* | Not known: | depression, sleep disturbances |

The dose dependent adverse events of hydrochlorothiazide (particularly electrolyte disturbances) may increase when titrating the hydrochlorothiazide.

### 4.9 Overdose

No specific information is available on the treatment of overdose with Irbesartan Hydrochlorothiazide BMS. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and/or gastric lavage. Activated charcoal may be useful in the treatment of overdose. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacements given quickly.

The most likely manifestations of irbesartan overdose are expected to be hypotension and tachycardia; bradycardia might also occur.

Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloremia, hyponatraemia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasms and/or accentuate cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic medicinal products.

Irbesartan is not removed by haemodialysis. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.



## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: angiotensin-II antagonists, combinations
ATC code: C09DA04.

Irbesartan Hydrochlorothiazide BMS is a combination of an angiotensin-II receptor antagonist, irbesartan, and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Irbesartan is a potent, orally active, selective angiotensin-II receptor ($AT_1$ subtype) 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 in patients without risk of electrolyte imbalance (see sections 4.4 and 4.5). 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.

Hydrochlorothiazide is a thiazide diuretic. The mechanism of antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity, increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. Presumably through blockade of the renin-angiotensin-aldosterone system, co-administration of irbesartan tends to reverse the potassium loss associated with these diuretics. With hydrochlorothiazide, onset of diuresis occurs in 2 hours, and peak effect occurs at about 4 hours, while the action persists for approximately 6-12 hours.

The combination of hydrochlorothiazide and irbesartan produces dose-related additive reductions in blood pressure across their therapeutic dose ranges. The addition of 12.5 mg hydrochlorothiazide to 300 mg irbesartan once daily in patients not adequately controlled on 300 mg irbesartan alone resulted in further placebo-corrected diastolic blood pressure reductions at trough (24 hours post-dosing) of 6.1 mm Hg. The combination of 300 mg irbesartan and 12.5 mg hydrochlorothiazide resulted in an overall placebo-subtracted systolic/diastolic reductions of up to 13.6/11.5 mm Hg.

Limited clinical data (7 out of 22 patients) suggest that patients not controlled with the 300 mg/12.5 mg combination may respond when uptitrated to 300 mg/25 mg. In these patients, an incremental blood pressure lowering effect was observed for both systolic blood pressure (SBP) and diastolic blood pressure (DBP) (13.3 and 8.3 mm Hg, respectively).

Once daily dosing with 150 mg irbesartan and 12.5 mg hydrochlorothiazide gave systolic/diastolic mean placebo-adjusted blood pressure reductions at trough (24 hours post-dosing) of 12.9/6.9 mm Hg in patients with mild-to-moderate hypertension. Peak effects occurred at 3-6 hours. When assessed by ambulatory blood pressure monitoring, the combination 150 mg irbesartan and 12.5 mg hydrochlorothiazide once daily produced consistent reduction in blood pressure over the 24 hours period with mean 24-hour placebo-subtracted systolic/diastolic reductions of 15.8/10.0 mm Hg. When measured by ambulatory blood pressure monitoring, the trough to peak effects of Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg were 100%. The trough to peak effects measured by cuff during office visits were 68% and 76% for Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg and Irbesartan Hydrochlorothiazide BMS 300 mg/12.5 mg, respectively. These 24-hour effects were observed without excessive blood pressure lowering at peak and are consistent with safe and effective blood-pressure lowering over the once-daily dosing interval.

In patients not adequately controlled on 25 mg hydrochlorothiazide alone, the addition of irbesartan gave an added placebo-subtracted systolic/diastolic mean reduction of 11.1/7.2 mm Hg.

The blood pressure lowering effect of irbesartan in combination with hydrochlorothiazide is apparent after the first dose and substantially present within 1-2 weeks, with the maximal effect occurring by 6-8 weeks. In long-term follow-up studies, the effect of irbesartan/hydrochlorothiazide was maintained for over one year. Although not specifically studied with the Irbesartan Hydrochlorothiazide BMS, rebound hypertension has not been seen with either irbesartan or hydrochlorothiazide.

The effect of the combination of irbesartan and hydrochlorothiazide on morbidity and mortality has not been studied. Epidemiological studies have shown that long term treatment with hydrochlorothiazide reduces the risk of cardiovascular mortality and morbidity.

There is no difference in response to Irbesartan Hydrochlorothiazide BMS, regardless of 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 non-black patients.

Efficacy and safety of Irbesartan Hydrochlorothiazide BMS as initial therapy for severe hypertension (defined as SeDBP ≥ 110 mmHg) was evaluated in a multicenter, randomized, double-blind, active-

controlled, 8-week, parallel-arm study. A total of 697 patients were randomized in a 2:1 ratio to either irbesartan/hydrochlorothiazide 150 mg/12.5 mg or to irbesartan 150 mg and systematically force-titrated (before assessing the response to the lower dose) after one week to irbesartan/hydrochlorothiazide 300 mg/25 mg or irbesartan 300 mg, respectively.

The study recruited 58% males. The mean age of patients was 52.5 years, 13% were ≥ 65 years of age, and just 2% were ≥ 75 years of age. Twelve percent (12%) of patients were diabetic, 34% were hyperlipidemic and the most frequent cardiovascular condition was stable angina pectoris in 3.5% of the participants.

The primary objective of this study was to compare the proportion of patients whose SeDBP was controlled (SeDBP < 90 mmHg) at Week 5 of treatment. Forty-seven percent (47.2%) of patients on the combination achieved trough SeDBP < 90 mmHg compared to 33.2% of patients on irbesartan ($p = 0.0005$). The mean baseline blood pressure was approximately 172/113 mmHg in each treatment group and decreases of SeSBP/SeDBP at five weeks were 30.8/24.0 mmHg and 21.1/19.3 mmHg for irbesartan/hydrochlorothiazide and irbesartan, respectively ($p < 0.0001$).

The types and incidences of adverse events reported for patients treated with the combination were similar to the adverse event profile for patients on monotherapy. During the 8-week treatment period, there were no reported cases of syncope in either treatment group. There were 0.6% and 0% of patients with hypotension and 2.8% and 3.1% of patients with dizziness as adverse reactions reported in the combination and monotherapy groups, respectively.



## 5.2 Pharmacokinetic properties

Concomitant administration of hydrochlorothiazide and irbesartan has no effect on the pharmacokinetics of either medicinal product.

Irbesartan and hydrochlorothiazide are orally active agents and do not require biotransformation for their activity. Following oral administration of Irbesartan Hydrochlorothiazide BMS, the absolute oral bioavailability is 60-80% and 50-80% for irbesartan and hydrochlorothiazide, respectively. Food does not affect the bioavailability of Irbesartan Hydrochlorothiazide BMS. Peak plasma concentration occurs at 1.5-2 hours after oral administration for irbesartan and 1-2.5 hours for hydrochlorothiazide.

Plasma protein binding of irbesartan is approximately 96%, with negligible binding to cellular blood components. The volume of distribution for irbesartan is 53-93 litres. Hydrochlorothiazide is 68% protein-bound in the plasma, and its apparent volume of distribution is 0.83-1.14 l/kg.

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 was observed; the mechanism for this is unknown. The total body and renal clearance are 157-176 and 3.0-3.5 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. The mean plasma half-life of hydrochlorothiazide reportedly ranges from 5-15 hours.

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 and its metabolites are eliminated by both biliary and renal pathways. After either oral or intravenous

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. Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidneys. At least 61% of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier, and is excreted in breast milk.

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. In patients with creatinine clearance < 20 ml/min, the elimination half-life of hydrochlorothiazide was reported to increase to 21 hours.

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

Irbesartan/hydrochlorothiazide: the potential toxicity of the irbesartan/hydrochlorothiazide combination after oral administration was evaluated in rats and macaques in studies lasting up to 6 months. There were no toxicological findings observed of relevance to human therapeutic use. The following changes, observed in rats and macaques receiving the irbesartan/hydrochlorothiazide combination at 10/10 and 90/90 mg/kg/day, were also seen with one of the two medicinal products alone and/or were secondary to decreases in blood pressure (no significant toxicologic interactions were observed):

- kidney changes, characterized by slight increases in serum urea and creatinine, and hyperplasia/hypertrophy of the juxtaglomerular apparatus, which are a direct consequence of the interaction of irbesartan with the renin-angiotensin system;
- slight decreases in erythrocyte parameters (erythrocytes, haemoglobin, haematocrit);
- stomach discoloration, ulcers and focal necrosis of gastric mucosa were observed in few rats in a 6 months toxicity study at irbesartan 90 mg/kg/day, hydrochlorothiazide 90 mg/kg/day, and irbesartan/hydrochlorothiazide 10/10 mg/kg/day. These lesions were not observed in macaques;
- decreases in serum potassium due to hydrochlorothiazide and partly prevented when hydrochlorothiazide was given in combination with irbesartan.

Most of the above mentioned effects appear to be due to the pharmacological activity of irbesartan (blockade of angiotensin-II-induced inhibition of renin release, with stimulation of the renin-producing cells) and occur also with angiotensin converting enzyme inhibitors. These findings appear to have no relevance to the use of therapeutic doses of irbesartan/hydrochlorothiazide in humans.



No teratogenic effects were seen in rats given irbesartan and hydrochlorothiazide in combination at doses that produced maternal toxicity. The effects of the irbesartan/hydrochlorothiazide combination on fertility have not been evaluated in animal studies, as there is no evidence of adverse effect on fertility in animals or humans with either irbesartan or hydrochlorothiazide when administered alone. However, another angiotensin-II antagonist affected fertility parameters in animal studies when given alone. These findings were also observed with lower doses of this other angiotensin-II antagonist when given in combination with hydrochlorothiazide.

There was no evidence of mutagenicity or clastogenicity with the irbesartan/hydrochlorothiazide combination. The carcinogenic potential of irbesartan and hydrochlorothiazide in combination has not been evaluated in animal studies.

Irbesartan: 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 kidneys (such as interstitial nephritis, tubular distention, 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 was noted at doses causing significant maternal toxicity, including mortality. No teratogenic effects were observed in the rat or rabbit.

Hydrochlorothiazide: although equivocal evidence for a genotoxic or carcinogenic effect was found in some experimental models, the extensive human experience with hydrochlorothiazide has failed to show an association between its use and an increase in neoplasms.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet core:
Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Pregelatinized starch
Silicon dioxide
Magnesium stearate
Red and yellow ferric oxides

Film-coating:
Lactose monohydrate
Hypromellose
Titanium dioxide
Macrogol 3350
Red and black ferric oxides
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.
Store in the original package in order to protect from moisture.

### 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 tablets; 7 blister cards of 8 x 1 film-coated tablets 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/1/06/369/023-028

## 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

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

Sanofi Winthrop Industrie
30-36, avenue Gustave Eiffel
37100 Tours
France

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 Hydrochlorothiazide BMS is aligned with the cross-referred product, KARVEZIDE, 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 Hydrochlorothiazide BMS 150 mg/12.5 mg tablets
irbesartan/hydrochlorothiazide

## 2. STATEMENT OF ACTIVE SUBSTANCES

Each tablet contains: irbesartan 150 mg and hydrochlorothiazide 12.5 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.
Store in the original package in order to protect from moisture.

## 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 NUMBERS

EU/1/06/369/001 - 14 tablets
EU/1/06/369/002 - 28 tablets
EU/1/06/369/003 - 56 tablets
EU/1/06/369/004 - 56 x 1 tablets
EU/1/06/369/005 - 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 Hydrochlorothiazide BMS 150 mg/12.5 mg

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

**1. NAME OF THE MEDICINAL PRODUCT**

Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg tablets
irbesartan/hydrochlorothiazide

**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 Hydrochlorothiazide BMS 300 mg/12.5 mg tablets
irbesartan/hydrochlorothiazide

## 2. STATEMENT OF ACTIVE SUBSTANCES

Each tablet contains: irbesartan 300 mg and hydrochlorothiazide 12.5 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.
Store in the original package in order to protect from moisture.

## 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 NUMBERS

EU/1/06/369/006 - 14 tablets
EU/1/06/369/007 - 28 tablets
EU/1/06/369/008 - 56 tablets
EU/1/06/369/009 - 56 x 1 tablets
EU/1/06/369/010 - 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 Hydrochlorothiazide BMS 300 mg/12.5 mg

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

**1. NAME OF THE MEDICINAL PRODUCT**

Irbesartan Hydrochlorothiazide BMS 300 mg/12.5 mg tablets
irbesartan/hydrochlorothiazide

**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 Hydrochlorothiazide BMS 150 mg/12.5 mg film-coated tablets
irbesartan/hydrochlorothiazide

## 2. STATEMENT OF ACTIVE SUBSTANCES

Each tablet contains: irbesartan 150 mg and hydrochlorothiazide 12.5 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.
Store in the original package in order to protect from moisture.

## 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 NUMBERS

EU/1/06/369/011 - 14 tablets
EU/1/06/369/012 - 28 tablets
EU/1/06/369/013 - 56 tablets
EU/1/06/369/014 - 56 x 1 tablets
EU/1/06/369/015 - 84 tablets
EU/1/06/369/016 - 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 Hydrochlorothiazide BMS 150 mg/12.5 mg

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

**1. NAME OF THE MEDICINAL PRODUCT**

Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg tablets
irbesartan/hydrochlorothiazide

**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 Hydrochlorothiazide BMS 300 mg/12.5 mg film-coated tablets
irbesartan/hydrochlorothiazide

## 2. STATEMENT OF ACTIVE SUBSTANCES

Each tablet contains: irbesartan 300 mg and hydrochlorothiazide 12.5 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.
Store in the original package in order to protect from moisture.

## 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 NUMBERS

EU/1/06/369/017 - 14 tablets
EU/1/06/369/018 - 28 tablets
EU/1/06/369/019 - 56 tablets
EU/1/06/369/020 - 56 x 1 tablets
EU/1/06/369/021 - 84 tablets
EU/1/06/369/022 - 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 Hydrochlorothiazide BMS 300 mg/12.5 mg

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

**1. NAME OF THE MEDICINAL PRODUCT**

Irbesartan Hydrochlorothiazide BMS 300 mg/12.5 mg tablets
irbesartan/hydrochlorothiazide

**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 Hydrochlorothiazide BMS 300 mg/25 mg film-coated tablets
irbesartan/hydrochlorothiazide

## 2. STATEMENT OF ACTIVE SUBSTANCES

Each tablet contains: irbesartan 300 mg and hydrochlorothiazide 25 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.
Store in the original package in order to protect from moisture.

## 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 NUMBERS

EU/1/06/369/023 - 14 tablets
EU/1/06/369/024 - 28 tablets
EU/1/06/369/025 - 56 tablets
EU/1/06/369/026 - 56 x 1 tablets
EU/1/06/369/027 - 84 tablets
EU/1/06/369/028 - 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 Hydrochlorothiazide BMS 300 mg/25 mg

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

**1. NAME OF THE MEDICINAL PRODUCT**

Irbesartan Hydrochlorothiazide BMS 300 mg/25 mg tablets
irbesartan/hydrochlorothiazide

**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 Hydrochlorothiazide BMS 150 mg/12.5 mg tablets**
irbesartan/hydrochlorothiazide

**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 HYDROCHLOROTHIAZIDE BMS IS AND WHAT IT IS USED FOR

Irbesartan Hydrochlorothiazide BMS is a combination of two active substances, irbesartan and hydrochlorothiazide.
Irbesartan belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin-II is a substance produced in the body that binds to receptors in blood vessels causing them to tighten. This results in an increase in blood pressure. Irbesartan prevents the binding of angiotensin-II to these receptors, causing the blood vessels to relax and the blood pressure to lower. Hydrochlorothiazide is one of a group of medicines (called thiazide diuretics) that causes increased urine output and so causes a lowering of blood pressure.
The two active ingredients in Irbesartan Hydrochlorothiazide BMS work together to lower blood pressure further than if either was given alone.

**Irbesartan Hydrochlorothiazide BMS is used to treat high blood pressure**, when treatment with irbesartan or hydrochlorothiazide alone did not provide adequate control of your blood pressure.

## 2. BEFORE YOU TAKE IRBESARTAN HYDROCHLOROTHIAZIDE BMS

**Do not take Irbesartan Hydrochlorothiazide BMS**
- if you are **allergic** (hypersensitive) to irbesartan or any of the other ingredients of Irbesartan Hydrochlorothiazide BMS
- if you are **allergic** (hypersensitive) to hydrochlorothiazide or any other sulfonamide-derived medicines
- if you are **more than 3 months pregnant**. (It is also better to avoid Irbesartan Hydrochlorothiazide BMS in early pregnancy – see pregnancy section)
- if you have **severe liver** or **kidney problems**
- if you have **difficulty in producing urine**
- if your doctor determines that you have **persistently high calcium or low potassium levels in your blood**

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

**Take special care with Irbesartan Hydrochlorothiazide 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** or have a **kidney transplant**
- if you suffer from **heart problems**
- if you suffer from **liver problems**
- if you suffer from **diabetes**
- if you suffer from **lupus erythematosus** (also known as lupus or SLE)
- if you suffer from **primary aldosteronism** (a condition related to high production of the hormone aldosterone, which causes sodium retention and, in turn, an increase in blood pressure).

You must tell your doctor if you think you are (or might become) pregnant. Irbesartan Hydrochlorothiazide 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).

**You should also tell your doctor:**
- if you are on a **low-salt diet**
- if you have signs such as **abnormal thirst**, **dry mouth**, **general weakness**, **drowsiness**, **muscle pain or cramps**, **nausea**, **vomiting**, or an **abnormally fast heart beat** which may indicate an excessive effect of hydrochlorothiazide (contained in Irbesartan Hydrochlorothiazide BMS)
- if you experience an increased **sensitivity of the skin to the sun** with symptoms of sunburn (such as redness, itching, swelling, blistering) occurring more quickly than normal
- if you are **going to have an operation** (surgery) or **be given anaesthetics**

The hydrochlorothiazide contained in this medicine could produce a positive result in an anti-doping test.

**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.

Diuretic agents such as the hydrochlorothiazide contained in Irbesartan Hydrochlorothiazide BMS may have an effect on other medicines. Preparations containing lithium should not be taken with Irbesartan Hydrochlorothiazide BMS without close supervision by your doctor.

**You may need to have blood checks if you take:**
- potassium supplements
- salt substitutes containing potassium
- potassium sparing medicines or other diuretics (water tablets)
- some laxatives
- medicines for the treatment of gout
- therapeutic vitamin D supplements
- medicines to control heart rhythm
- medicines for diabetes (oral agents or insulins)

It is also important to tell your doctor if you are taking other medicines to reduce your blood pressure, steroids, medicines to treat cancer, pain killers or arthritis medicines.

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

Due to the hydrochlorothiazide contained in Irbesartan Hydrochlorothiazide BMS, if you drink alcohol while on treatment with this medicine, you may have an increased feeling of dizziness on standing up, specially when getting up from a sitting position.

**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 Hydrochlorothiazide 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 Hydrochlorothiazide BMS. Irbesartan Hydrochlorothiazide 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 Hydrochlorothiazide 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 Hydrochlorothiazide 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 Hydrochlorothiazide BMS**
**Irbesartan Hydrochlorothiazide 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 HYDROCHLOROTHIAZIDE BMS

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

**Dosage**
The usual dose of Irbesartan Hydrochlorothiazide BMS is one or two tablets a day. Irbesartan Hydrochlorothiazide BMS will usually be prescribed by your doctor when your previous treatment did not reduce your blood pressure enough. Your doctor will instruct you how to switch from the previous treatment to Irbesartan Hydrochlorothiazide BMS.

**Method of administration**
Irbesartan Hydrochlorothiazide BMS is for **oral use**. Swallow the tablets with a sufficient amount of fluid (e.g. one glass of water). You can take Irbesartan Hydrochlorothiazide 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 Hydrochlorothiazide BMS until your doctor tells you otherwise.

The maximal blood pressure lowering effect should be reached 6-8 weeks after beginning treatment.

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

**Children should not take Irbesartan Hydrochlorothiazide BMS**
Irbesartan Hydrochlorothiazide 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 Hydrochlorothiazide 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 Hydrochlorothiazide BMS can cause side effects, although not everybody gets them.
Some of these effects may be serious and may require medical attention.

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 the above symptoms or get short of breath,** stop taking Irbesartan Hydrochlorothiazide BMS and contact your doctor immediately.

Side effects reported in clinical studies for patients treated with Irbesartan Hydrochlorothiazide BMS were:

**Common side effects** *(affect 1 to 10 users in 100)*
- nausea/vomiting
- abnormal urination
- fatigue
- dizziness (including when getting up from a lying or sitting position)
- blood tests may show raised levels of an enzyme that measures the muscle and heart function (creatine kinase) or raised levels of substances that measure kidney function (blood urea nitrogen, creatinine).

**If any of these side effects causes you problems**, talk to your doctor.

**Uncommon side effects** *(affect 1 to 10 users in 1,000)*
- diarrhoea
- low blood pressure
- fainting
- heart rate increased
- flushing
- swelling
- sexual dysfunction (problems with sexual performance)
- blood tests may show lowered levels of potassium and sodium in your blood.

**If any of these side effects causes you problems**, talk to your doctor.

**Side effects reported since the launch of Irbesartan Hydrochlorothiazide BMS**
The frequency of these effects is not known. These undesirable effects are: headache, ringing in the ears, cough, taste disturbance, indigestion, pain in joints and muscles, liver function abnormal and impaired kidney function, increased level of potassium in your blood and allergic reactions such as rash, hives, swelling of the face, lips, mouth, tongue or throat.

As for any combination of two active substances, side effects associated with each individual component cannot be excluded.
**Side effects associated with irbesartan alone**
In addition to the side effects listed above, chest pain has also been reported.
**Side effects associated with hydrochlorothiazide alone**
Loss of appetite; stomach irritation; stomach cramps; constipation; jaundice (yellowing of the skin and/or whites of the eyes); inflammation of the pancreas characterised by severe upper stomach pain, often with nausea and vomiting; sleep disorders; depression; blurred vision; lack of white blood cells, which can result in frequent infections, fever; decrease in the number of platelets (a blood cell essential for the clotting of the blood), decreased number of red blood cells (anaemia) characterised by tiredness, headaches, being short of breath when exercising, dizziness and looking pale; kidney disease; lung problems including pneumonia or build-up of fluid in the lungs; increased sensitivity of the skin to the sun; inflammation of blood vessels; a skin disease characterized by the peeling of the skin all over the body; cutaneous lupus erythematosus, which is identified by a rash that may appear

on the face, neck, and scalp; allergic reactions; weakness and muscle spasm; altered heart rate; reduced blood pressure after a change in body position; swelling of the salivary glands; high sugar levels in the blood; sugar in the urine; increases in some kinds of blood fat; high uric acid levels in the blood, which may cause gout.

It is known that side effects associated with hydrochlorothiazide may increase with higher doses of hydrochlorothiazide.

**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 HYDROCHLOROTHIAZIDE BMS

Keep out of the reach and sight of children.

Do not use Irbesartan Hydrochlorothiazide 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.

Store in the original package in order to protect from moisture.

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 Hydrochlorothiazide BMS contains**

- The active substances are irbesartan and hydrochlorothiazide. Each tablet of Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg contains 150 mg irbesartan and 12.5 mg hydrochlorothiazide.
- The other ingredients are microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, magnesium stearate, colloidal hydrated silica, pregelatinised maize starch, red and yellow ferric oxides (E172).

**What Irbesartan Hydrochlorothiazide BMS looks like and contents of the pack**
Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg tablets are peach, biconvex, oval-shaped, with a heart debossed on one side and the number 2775 engraved on the other side.

Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg tablets are supplied in blister packs of 14, 28, 56 or 98 tablets. Unit dose blister packs of 56 x 1 tablet for delivery in hospitals are also available.

Not all pack sizes may be marketed.

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**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 Hydrochlorothiazide BMS 300 mg/12.5 mg tablets**
irbesartan/hydrochlorothiazide

**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 HYDROCHLOROTHIAZIDE BMS IS AND WHAT IT IS USED FOR

Irbesartan Hydrochlorothiazide BMS is a combination of two active substances, irbesartan and hydrochlorothiazide.
Irbesartan belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin-II is a substance produced in the body that binds to receptors in blood vessels causing them to tighten. This results in an increase in blood pressure. Irbesartan prevents the binding of angiotensin-II to these receptors, causing the blood vessels to relax and the blood pressure to lower. Hydrochlorothiazide is one of a group of medicines (called thiazide diuretics) that causes increased urine output and so causes a lowering of blood pressure.
The two active ingredients in Irbesartan Hydrochlorothiazide BMS work together to lower blood pressure further than if either was given alone.

**Irbesartan Hydrochlorothiazide BMS is used to treat high blood pressure**, when treatment with irbesartan or hydrochlorothiazide alone did not provide adequate control of your blood pressure.

## 2. BEFORE YOU TAKE IRBESARTAN HYDROCHLOROTHIAZIDE BMS

**Do not take Irbesartan Hydrochlorothiazide BMS**
- if you are **allergic** (hypersensitive) to irbesartan or any of the other ingredients of Irbesartan Hydrochlorothiazide BMS
- if you are **allergic** (hypersensitive) to hydrochlorothiazide or any other sulfonamide-derived medicines
- if you are **more than 3 months pregnant**. (It is also better to avoid Irbesartan Hydrochlorothiazide BMS in early pregnancy – see pregnancy section)
- if you have **severe liver** or **kidney problems**
- if you have **difficulty in producing urine**
- if your doctor determines that you have **persistently high calcium or low potassium levels in your blood**

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

**Take special care with Irbesartan Hydrochlorothiazide 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** or have a **kidney transplant**
- if you suffer from **heart problems**
- if you suffer from **liver problems**
- if you suffer from **diabetes**
- if you suffer from **lupus erythematosus** (also known as lupus or SLE)
- if you suffer from **primary aldosteronism** (a condition related to high production of the hormone aldosterone, which causes sodium retention and, in turn, an increase in blood pressure).

You must tell your doctor if you think you are (or might become) pregnant. Irbesartan Hydrochlorothiazide 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).

**You should also tell your doctor:**
- if you are on a **low-salt diet**
- if you have signs such as **abnormal thirst**, **dry mouth**, **general weakness**, **drowsiness**, **muscle pain or cramps**, **nausea**, **vomiting**, or an **abnormally fast heart beat** which may indicate an excessive effect of hydrochlorothiazide (contained in Irbesartan Hydrochlorothiazide BMS)
- if you experience an increased **sensitivity of the skin to the sun** with symptoms of sunburn (such as redness, itching, swelling, blistering) occurring more quickly than normal
- if you are **going to have an operation** (surgery) or **be given anaesthetics**

The hydrochlorothiazide contained in this medicine could produce a positive result in an anti-doping test.

**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.

Diuretic agents such as the hydrochlorothiazide contained in Irbesartan Hydrochlorothiazide BMS may have an effect on other medicines. Preparations containing lithium should not be taken with Irbesartan Hydrochlorothiazide BMS without close supervision by your doctor.

**You may need to have blood checks if you take:**
- potassium supplements
- salt substitutes containing potassium
- potassium sparing medicines or other diuretics (water tablets)
- some laxatives
- medicines for the treatment of gout
- therapeutic vitamin D supplements
- medicines to control heart rhythm
- medicines for diabetes (oral agents or insulins)

It is also important to tell your doctor if you are taking other medicines to reduce your blood pressure, steroids, medicines to treat cancer, pain killers or arthritis medicines.

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

Due to the hydrochlorothiazide contained in Irbesartan Hydrochlorothiazide BMS, if you drink alcohol while on treatment with this medicine, you may have an increased feeling of dizziness on standing up, specially when getting up from a sitting position.

**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 Hydrochlorothiazide 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 Hydrochlorothiazide BMS. Irbesartan Hydrochlorothiazide 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 Hydrochlorothiazide 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 Hydrochlorothiazide 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 Hydrochlorothiazide BMS**
**Irbesartan Hydrochlorothiazide 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 HYDROCHLOROTHIAZIDE BMS

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

**Dosage**
The usual dose of Irbesartan Hydrochlorothiazide BMS is one tablet a day. Irbesartan Hydrochlorothiazide BMS will usually be prescribed by your doctor when your previous treatment did not reduce your blood pressure enough. Your doctor will instruct you how to switch from the previous treatment to Irbesartan Hydrochlorothiazide BMS.

**Method of administration**
Irbesartan Hydrochlorothiazide BMS is for **oral use**. Swallow the tablets with a sufficient amount of fluid (e.g. one glass of water). You can take Irbesartan Hydrochlorothiazide 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 Hydrochlorothiazide BMS until your doctor tells you otherwise.

The maximal blood pressure lowering effect should be reached 6-8 weeks after beginning treatment.

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

**Children should not take Irbesartan Hydrochlorothiazide BMS**
Irbesartan Hydrochlorothiazide 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 Hydrochlorothiazide 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 Hydrochlorothiazide BMS can cause side effects, although not everybody gets them.
Some of these effects may be serious and may require medical attention.

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 the above symptoms or get short of breath,** stop taking Irbesartan Hydrochlorothiazide BMS and contact your doctor immediately.

Side effects reported in clinical studies for patients treated with Irbesartan Hydrochlorothiazide BMS were:

**Common side effects** *(affect 1 to 10 users in 100)*
- nausea/vomiting
- abnormal urination
- fatigue
- dizziness (including when getting up from a lying or sitting position)
- blood tests may show raised levels of an enzyme that measures the muscle and heart function (creatine kinase) or raised levels of substances that measure kidney function (blood urea nitrogen, creatinine).

**If any of these side effects causes you problems**, talk to your doctor.

**Uncommon side effects** *(affect 1 to 10 users in 1,000)*
- diarrhoea
- low blood pressure
- fainting
- heart rate increased
- flushing
- swelling
- sexual dysfunction (problems with sexual performance)
- blood tests may show lowered levels of potassium and sodium in your blood.

**If any of these side effects causes you problems**, talk to your doctor.

**Side effects reported since the launch of Irbesartan Hydrochlorothiazide BMS**
The frequency of these effects is not known. These undesirable effects are: headache, ringing in the ears, cough, taste disturbance, indigestion, pain in joints and muscles, liver function abnormal and impaired kidney function, increased level of potassium in your blood and allergic reactions such as rash, hives, swelling of the face, lips, mouth, tongue or throat.

As for any combination of two active substances, side effects associated with each individual component cannot be excluded.
**Side effects associated with irbesartan alone**
In addition to the side effects listed above, chest pain has also been reported.
**Side effects associated with hydrochlorothiazide alone**
Loss of appetite; stomach irritation; stomach cramps; constipation; jaundice (yellowing of the skin and/or whites of the eyes); inflammation of the pancreas characterised by severe upper stomach pain, often with nausea and vomiting; sleep disorders; depression; blurred vision; lack of white blood cells, which can result in frequent infections, fever; decrease in the number of platelets (a blood cell essential for the clotting of the blood), decreased number of red blood cells (anaemia) characterised by tiredness, headaches, being short of breath when exercising, dizziness and looking pale; kidney disease; lung problems including pneumonia or build-up of fluid in the lungs; increased sensitivity of the skin to the sun; inflammation of blood vessels; a skin disease characterized by the peeling of the skin all over the body; cutaneous lupus erythematosus, which is identified by a rash that may appear

on the face, neck, and scalp; allergic reactions; weakness and muscle spasm; altered heart rate; reduced blood pressure after a change in body position; swelling of the salivary glands; high sugar levels in the blood; sugar in the urine; increases in some kinds of blood fat; high uric acid levels in the blood, which may cause gout.

It is known that side effects associated with hydrochlorothiazide may increase with higher doses of hydrochlorothiazide.

**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 HYDROCHLOROTHIAZIDE BMS

Keep out of the reach and sight of children.

Do not use Irbesartan Hydrochlorothiazide 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.

Store in the original package in order to protect from moisture.

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 Hydrochlorothiazide BMS contains**

- The active substances are irbesartan and hydrochlorothiazide. Each tablet of Irbesartan Hydrochlorothiazide BMS 300 mg/12.5 mg contains 300 mg irbesartan and 12.5 mg hydrochlorothiazide.
- The other ingredients are microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, magnesium stearate, colloidal hydrated silica, pregelatinised maize starch, red and yellow ferric oxides (E172).

**What Irbesartan Hydrochlorothiazide BMS looks like and contents of the pack**
Irbesartan Hydrochlorothiazide BMS 300 mg/12.5 mg tablets are peach, biconvex, oval-shaped, with a heart debossed on one side and the number 2776 engraved on the other side.

Irbesartan Hydrochlorothiazide BMS 300 mg/12.5 mg tablets are supplied in blister packs of 14, 28, 56 or 98 tablets. Unit dose blister packs of 56 x 1 tablet for delivery in hospitals are also available.

Not all pack sizes may be marketed.

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**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 Hydrochlorothiazide BMS 150 mg/12.5 mg film-coated tablets**
irbesartan/hydrochlorothiazide

**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 HYDROCHLOROTHIAZIDE BMS IS AND WHAT IT IS USED FOR

Irbesartan Hydrochlorothiazide BMS is a combination of two active substances, irbesartan and hydrochlorothiazide.
Irbesartan belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin-II is a substance produced in the body that binds to receptors in blood vessels causing them to tighten. This results in an increase in blood pressure. Irbesartan prevents the binding of angiotensin-II to these receptors, causing the blood vessels to relax and the blood pressure to lower. Hydrochlorothiazide is one of a group of medicines (called thiazide diuretics) that causes increased urine output and so causes a lowering of blood pressure.
The two active ingredients in Irbesartan Hydrochlorothiazide BMS work together to lower blood pressure further than if either was given alone.

**Irbesartan Hydrochlorothiazide BMS is used to treat high blood pressure**, when treatment with irbesartan or hydrochlorothiazide alone did not provide adequate control of your blood pressure.

## 2. BEFORE YOU TAKE IRBESARTAN HYDROCHLOROTHIAZIDE BMS

**Do not take Irbesartan Hydrochlorothiazide BMS**
- if you are **allergic** (hypersensitive) to irbesartan or any of the other ingredients of Irbesartan Hydrochlorothiazide BMS
- if you are **allergic** (hypersensitive) to hydrochlorothiazide or any other sulfonamide-derived medicines
- if you are **more than 3 months pregnant**. (It is also better to avoid Irbesartan Hydrochlorothiazide BMS in early pregnancy – see pregnancy section)
- if you have **severe liver** or **kidney problems**
- if you have **difficulty in producing urine**
- if your doctor determines that you have **persistently high calcium or low potassium levels in your blood**

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

**Take special care with Irbesartan Hydrochlorothiazide 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** or have a **kidney transplant**
- if you suffer from **heart problems**
- if you suffer from **liver problems**
- if you suffer from **diabetes**
- if you suffer from **lupus erythematosus** (also known as lupus or SLE)
- if you suffer from **primary aldosteronism** (a condition related to high production of the hormone aldosterone, which causes sodium retention and, in turn, an increase in blood pressure).

You must tell your doctor if you think you are (or might become) pregnant. Irbesartan Hydrochlorothiazide 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).

**You should also tell your doctor:**
- if you are on a **low-salt diet**
- if you have signs such as **abnormal thirst**, **dry mouth**, **general weakness**, **drowsiness**, **muscle pain or cramps**, **nausea**, **vomiting**, or an **abnormally fast heart beat** which may indicate an excessive effect of hydrochlorothiazide (contained in Irbesartan Hydrochlorothiazide BMS)
- if you experience an increased **sensitivity of the skin to the sun** with symptoms of sunburn (such as redness, itching, swelling, blistering) occurring more quickly than normal
- if you are **going to have an operation** (surgery) or **be given anaesthetics**

The hydrochlorothiazide contained in this medicine could produce a positive result in an anti-doping test.

**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.

Diuretic agents such as the hydrochlorothiazide contained in Irbesartan Hydrochlorothiazide BMS may have an effect on other medicines. Preparations containing lithium should not be taken with Irbesartan Hydrochlorothiazide BMS without close supervision by your doctor.

**You may need to have blood checks if you take:**
- potassium supplements
- salt substitutes containing potassium
- potassium sparing medicines or other diuretics (water tablets)
- some laxatives
- medicines for the treatment of gout
- therapeutic vitamin D supplements
- medicines to control heart rhythm
- medicines for diabetes (oral agents or insulins)

It is also important to tell your doctor if you are taking other medicines to reduce your blood pressure, steroids, medicines to treat cancer, pain killers or arthritis medicines.

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

Due to the hydrochlorothiazide contained in Irbesartan Hydrochlorothiazide BMS, if you drink alcohol while on treatment with this medicine, you may have an increased feeling of dizziness on standing up, specially when getting up from a sitting position.

**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 Hydrochlorothiazide 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 Hydrochlorothiazide BMS. Irbesartan Hydrochlorothiazide 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 Hydrochlorothiazide 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 Hydrochlorothiazide 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 Hydrochlorothiazide BMS**
**Irbesartan Hydrochlorothiazide 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 HYDROCHLOROTHIAZIDE BMS

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

**Dosage**
The usual dose of Irbesartan Hydrochlorothiazide BMS is one or two tablets a day. Irbesartan Hydrochlorothiazide BMS will usually be prescribed by your doctor when your previous treatment did not reduce your blood pressure enough. Your doctor will instruct you how to switch from the previous treatment to Irbesartan Hydrochlorothiazide BMS.

**Method of administration**
Irbesartan Hydrochlorothiazide BMS is for **oral use**. Swallow the tablets with a sufficient amount of fluid (e.g. one glass of water). You can take Irbesartan Hydrochlorothiazide 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 Hydrochlorothiazide BMS until your doctor tells you otherwise.

The maximal blood pressure lowering effect should be reached 6-8 weeks after beginning treatment.

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

**Children should not take Irbesartan Hydrochlorothiazide BMS**
Irbesartan Hydrochlorothiazide 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 Hydrochlorothiazide 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 Hydrochlorothiazide BMS can cause side effects, although not everybody gets them.
Some of these effects may be serious and may require medical attention.

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 the above symptoms or get short of breath,** stop taking Irbesartan Hydrochlorothiazide BMS and contact your doctor immediately.

Side effects reported in clinical studies for patients treated with Irbesartan Hydrochlorothiazide BMS were:

**Common side effects** *(affect 1 to 10 users in 100)*
- nausea/vomiting
- abnormal urination
- fatigue
- dizziness (including when getting up from a lying or sitting position)
- blood tests may show raised levels of an enzyme that measures the muscle and heart function (creatine kinase) or raised levels of substances that measure kidney function (blood urea nitrogen, creatinine).

**If any of these side effects causes you problems**, talk to your doctor.

**Uncommon side effects** *(affect 1 to 10 users in 1,000)*
- diarrhoea
- low blood pressure
- fainting
- heart rate increased
- flushing
- swelling
- sexual dysfunction (problems with sexual performance)
- blood tests may show lowered levels of potassium and sodium in your blood.

**If any of these side effects causes you problems**, talk to your doctor.

**Side effects reported since the launch of Irbesartan Hydrochlorothiazide BMS**
The frequency of these effects is not known. These undesirable effects are: headache, ringing in the ears, cough, taste disturbance, indigestion, pain in joints and muscles, liver function abnormal and impaired kidney function, increased level of potassium in your blood and allergic reactions such as rash, hives, swelling of the face, lips, mouth, tongue or throat.

As for any combination of two active substances, side effects associated with each individual component cannot be excluded.
**Side effects associated with irbesartan alone**
In addition to the side effects listed above, chest pain has also been reported.
**Side effects associated with hydrochlorothiazide alone**
Loss of appetite; stomach irritation; stomach cramps; constipation; jaundice (yellowing of the skin and/or whites of the eyes); inflammation of the pancreas characterised by severe upper stomach pain, often with nausea and vomiting; sleep disorders; depression; blurred vision; lack of white blood cells, which can result in frequent infections, fever; decrease in the number of platelets (a blood cell essential for the clotting of the blood), decreased number of red blood cells (anaemia) characterised by tiredness, headaches, being short of breath when exercising, dizziness and looking pale; kidney disease; lung problems including pneumonia or build-up of fluid in the lungs; increased sensitivity of the skin to the sun; inflammation of blood vessels; a skin disease characterized by the peeling of the skin all over the body; cutaneous lupus erythematosus, which is identified by a rash that may appear

on the face, neck, and scalp; allergic reactions; weakness and muscle spasm; altered heart rate; reduced blood pressure after a change in body position; swelling of the salivary glands; high sugar levels in the blood; sugar in the urine; increases in some kinds of blood fat; high uric acid levels in the blood, which may cause gout.

It is known that side effects associated with hydrochlorothiazide may increase with higher doses of hydrochlorothiazide.

**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 HYDROCHLOROTHIAZIDE BMS

Keep out of the reach and sight of children.

Do not use Irbesartan Hydrochlorothiazide 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.

Store in the original package in order to protect from moisture.

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 Hydrochlorothiazide BMS contains**

- The active substances are irbesartan and hydrochlorothiazide. Each film-coated tablet of Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg contains 150 mg irbesartan and 12.5 mg hydrochlorothiazide.
- The other ingredients are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hypromellose, silicon dioxide, magnesium stearate, titanium dioxide, macrogol 3000, red and yellow ferric oxides, carnauba wax.

**What Irbesartan Hydrochlorothiazide BMS looks like and contents of the pack**
Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg film-coated tablets are peach, biconvex, oval-shaped, with a heart debossed on one side and the number 2875 engraved on the other side.

Irbesartan Hydrochlorothiazide BMS 150 mg/12.5 mg film-coated tablets are supplied in blister packs of 14, 28, 56, 84 or 98 film-coated tablets. Unit dose blister packs of 56 x 1 film-coated tablet for delivery in hospitals are also available.

Not all pack sizes may be marketed.

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**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 Hydrochlorothiazide BMS 300 mg/12.5 mg film-coated tablets**
irbesartan/hydrochlorothiazide

**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 HYDROCHLOROTHIAZIDE BMS IS AND WHAT IT IS USED FOR

Irbesartan Hydrochlorothiazide BMS is a combination of two active substances, irbesartan and hydrochlorothiazide.
Irbesartan belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin-II is a substance produced in the body that binds to receptors in blood vessels causing them to tighten. This results in an increase in blood pressure. Irbesartan prevents the binding of angiotensin-II to these receptors, causing the blood vessels to relax and the blood pressure to lower. Hydrochlorothiazide is one of a group of medicines (called thiazide diuretics) that causes increased urine output and so causes a lowering of blood pressure.
The two active ingredients in Irbesartan Hydrochlorothiazide BMS work together to lower blood pressure further than if either was given alone.

**Irbesartan Hydrochlorothiazide BMS is used to treat high blood pressure**, when treatment with irbesartan or hydrochlorothiazide alone did not provide adequate control of your blood pressure.

## 2. BEFORE YOU TAKE IRBESARTAN HYDROCHLOROTHIAZIDE BMS

**Do not take Irbesartan Hydrochlorothiazide BMS**
- if you are **allergic** (hypersensitive) to irbesartan or any of the other ingredients of Irbesartan Hydrochlorothiazide BMS
- if you are **allergic** (hypersensitive) to hydrochlorothiazide or any other sulfonamide-derived medicines
- if you are **more than 3 months pregnant**. (It is also better to avoid Irbesartan Hydrochlorothiazide BMS in early pregnancy – see pregnancy section)
- if you have **severe liver** or **kidney problems**
- if you have **difficulty in producing urine**
- if your doctor determines that you have **persistently high calcium or low potassium levels in your blood**

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

**Take special care with Irbesartan Hydrochlorothiazide 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** or have a **kidney transplant**
- if you suffer from **heart problems**
- if you suffer from **liver problems**
- if you suffer from **diabetes**
- if you suffer from **lupus erythematosus** (also known as lupus or SLE)
- if you suffer from **primary aldosteronism** (a condition related to high production of the hormone aldosterone, which causes sodium retention and, in turn, an increase in blood pressure).

You must tell your doctor if you think you are (or might become) pregnant. Irbesartan Hydrochlorothiazide 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).

**You should also tell your doctor:**
- if you are on a **low-salt diet**
- if you have signs such as **abnormal thirst**, **dry mouth**, **general weakness**, **drowsiness**, **muscle pain or cramps**, **nausea**, **vomiting**, or an **abnormally fast heart beat** which may indicate an excessive effect of hydrochlorothiazide (contained in Irbesartan Hydrochlorothiazide BMS)
- if you experience an increased **sensitivity of the skin to the sun** with symptoms of sunburn (such as redness, itching, swelling, blistering) occurring more quickly than normal
- if you are **going to have an operation** (surgery) or **be given anaesthetics**

The hydrochlorothiazide contained in this medicine could produce a positive result in an anti-doping test.

**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.

Diuretic agents such as the hydrochlorothiazide contained in Irbesartan Hydrochlorothiazide BMS may have an effect on other medicines. Preparations containing lithium should not be taken with Irbesartan Hydrochlorothiazide BMS without close supervision by your doctor.

**You may need to have blood checks if you take:**
- potassium supplements
- salt substitutes containing potassium
- potassium sparing medicines or other diuretics (water tablets)
- some laxatives
- medicines for the treatment of gout
- therapeutic vitamin D supplements
- medicines to control heart rhythm
- medicines for diabetes (oral agents or insulins)

It is also important to tell your doctor if you are taking other medicines to reduce your blood pressure, steroids, medicines to treat cancer, pain killers or arthritis medicines.

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

Due to the hydrochlorothiazide contained in Irbesartan Hydrochlorothiazide BMS, if you drink alcohol while on treatment with this medicine, you may have an increased feeling of dizziness on standing up, specially when getting up from a sitting position.

**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 Hydrochlorothiazide 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 Hydrochlorothiazide BMS. Irbesartan Hydrochlorothiazide 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 Hydrochlorothiazide 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 Hydrochlorothiazide 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 Hydrochlorothiazide BMS**
**Irbesartan Hydrochlorothiazide 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 HYDROCHLOROTHIAZIDE BMS

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

**Dosage**
The usual dose of Irbesartan Hydrochlorothiazide BMS is one tablet a day. Irbesartan Hydrochlorothiazide BMS will usually be prescribed by your doctor when your previous treatment did not reduce your blood pressure enough. Your doctor will instruct you how to switch from the previous treatment to Irbesartan Hydrochlorothiazide BMS.

**Method of administration**
Irbesartan Hydrochlorothiazide BMS is for **oral use**. Swallow the tablets with a sufficient amount of fluid (e.g. one glass of water). You can take Irbesartan Hydrochlorothiazide 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 Hydrochlorothiazide BMS until your doctor tells you otherwise.

The maximal blood pressure lowering effect should be reached 6-8 weeks after beginning treatment.

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

**Children should not take Irbesartan Hydrochlorothiazide BMS**
Irbesartan Hydrochlorothiazide 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 Hydrochlorothiazide 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 Hydrochlorothiazide BMS can cause side effects, although not everybody gets them.
Some of these effects may be serious and may require medical attention.

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 the above symptoms or get short of breath,** stop taking Irbesartan Hydrochlorothiazide BMS and contact your doctor immediately.

Side effects reported in clinical studies for patients treated with Irbesartan Hydrochlorothiazide BMS were:

**Common side effects** *(affect 1 to 10 users in 100)*
- nausea/vomiting
- abnormal urination
- fatigue
- dizziness (including when getting up from a lying or sitting position)
- blood tests may show raised levels of an enzyme that measures the muscle and heart function (creatine kinase) or raised levels of substances that measure kidney function (blood urea nitrogen, creatinine).

**If any of these side effects causes you problems**, talk to your doctor.

**Uncommon side effects** *(affect 1 to 10 users in 1,000)*
- diarrhoea
- low blood pressure
- fainting
- heart rate increased
- flushing
- swelling
- sexual dysfunction (problems with sexual performance)
- blood tests may show lowered levels of potassium and sodium in your blood.

**If any of these side effects causes you problems**, talk to your doctor.

**Side effects reported since the launch of Irbesartan Hydrochlorothiazide BMS**
The frequency of these effects is not known. These undesirable effects are: headache, ringing in the ears, cough, taste disturbance, indigestion, pain in joints and muscles, liver function abnormal and impaired kidney function, increased level of potassium in your blood and allergic reactions such as rash, hives, swelling of the face, lips, mouth, tongue or throat.



As for any combination of two active substances, side effects associated with each individual component cannot be excluded.
**Side effects associated with irbesartan alone**
In addition to the side effects listed above, chest pain has also been reported.
**Side effects associated with hydrochlorothiazide alone**
Loss of appetite; stomach irritation; stomach cramps; constipation; jaundice (yellowing of the skin and/or whites of the eyes); inflammation of the pancreas characterised by severe upper stomach pain, often with nausea and vomiting; sleep disorders; depression; blurred vision; lack of white blood cells, which can result in frequent infections, fever; decrease in the number of platelets (a blood cell essential for the clotting of the blood), decreased number of red blood cells (anaemia) characterised by tiredness, headaches, being short of breath when exercising, dizziness and looking pale; kidney disease; lung problems including pneumonia or build-up of fluid in the lungs; increased sensitivity of the skin to the sun; inflammation of blood vessels; a skin disease characterized by the peeling of the skin all over the body; cutaneous lupus erythematosus, which is identified by a rash that may appear

on the face, neck, and scalp; allergic reactions; weakness and muscle spasm; altered heart rate; reduced blood pressure after a change in body position; swelling of the salivary glands; high sugar levels in the blood; sugar in the urine; increases in some kinds of blood fat; high uric acid levels in the blood, which may cause gout.

It is known that side effects associated with hydrochlorothiazide may increase with higher doses of hydrochlorothiazide.

**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 HYDROCHLOROTHIAZIDE BMS

Keep out of the reach and sight of children.

Do not use Irbesartan Hydrochlorothiazide 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.

Store in the original package in order to protect from moisture.

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 Hydrochlorothiazide BMS contains**

- The active substances are irbesartan and hydrochlorothiazide. Each film-coated tablet of Irbesartan Hydrochlorothiazide BMS 300 mg/12.5 mg contains 300 mg irbesartan and 12.5 mg hydrochlorothiazide.
- The other ingredients are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hypromellose, silicon dioxide, magnesium stearate, titanium dioxide, macrogol 3000, red and yellow ferric oxides, carnauba wax.

**What Irbesartan Hydrochlorothiazide BMS looks like and contents of the pack**
Irbesartan Hydrochlorothiazide BMS 300 mg/12.5 mg film-coated tablets are peach, biconvex, oval-shaped, with a heart debossed on one side and the number 2876 engraved on the other side.

Irbesartan Hydrochlorothiazide BMS 300 mg/12.5 mg film-coated tablets are supplied in blister packs of 14, 28, 56, 84 or 98 film-coated tablets. Unit dose blister packs of 56 x 1 film-coated tablet for delivery in hospitals are also available.

Not all pack sizes may be marketed.

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**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 Hydrochlorothiazide BMS 300 mg/25 mg film-coated tablets**
irbesartan/hydrochlorothiazide

**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 HYDROCHLOROTHIAZIDE BMS IS AND WHAT IT IS USED FOR

Irbesartan Hydrochlorothiazide BMS is a combination of two active substances, irbesartan and hydrochlorothiazide.
Irbesartan belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin-II is a substance produced in the body that binds to receptors in blood vessels causing them to tighten. This results in an increase in blood pressure. Irbesartan prevents the binding of angiotensin-II to these receptors, causing the blood vessels to relax and the blood pressure to lower. Hydrochlorothiazide is one of a group of medicines (called thiazide diuretics) that causes increased urine output and so causes a lowering of blood pressure.
The two active ingredients in Irbesartan Hydrochlorothiazide BMS work together to lower blood pressure further than if either was given alone.

**Irbesartan Hydrochlorothiazide BMS is used to treat high blood pressure**, when treatment with irbesartan or hydrochlorothiazide alone did not provide adequate control of your blood pressure.

## 2. BEFORE YOU TAKE IRBESARTAN HYDROCHLOROTHIAZIDE BMS

**Do not take Irbesartan Hydrochlorothiazide BMS**
- if you are **allergic** (hypersensitive) to irbesartan or any of the other ingredients of Irbesartan Hydrochlorothiazide BMS
- if you are **allergic** (hypersensitive) to hydrochlorothiazide or any other sulfonamide-derived medicines
- if you are **more than 3 months pregnant**. (It is also better to avoid Irbesartan Hydrochlorothiazide BMS in early pregnancy – see pregnancy section)
- if you have **severe liver** or **kidney problems**
- if you have **difficulty in producing urine**
- if your doctor determines that you have **persistently high calcium or low potassium levels in your blood**

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

**Take special care with Irbesartan Hydrochlorothiazide 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** or have a **kidney transplant**
- if you suffer from **heart problems**
- if you suffer from **liver problems**
- if you suffer from **diabetes**
- if you suffer from **lupus erythematosus** (also known as lupus or SLE)
- if you suffer from **primary aldosteronism** (a condition related to high production of the hormone aldosterone, which causes sodium retention and, in turn, an increase in blood pressure).

You must tell your doctor if you think you are (or might become) pregnant. Irbesartan Hydrochlorothiazide 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).

**You should also tell your doctor:**
- if you are on a **low-salt diet**
- if you have signs such as **abnormal thirst**, **dry mouth**, **general weakness**, **drowsiness**, **muscle pain or cramps**, **nausea**, **vomiting**, or an **abnormally fast heart beat** which may indicate an excessive effect of hydrochlorothiazide (contained in Irbesartan Hydrochlorothiazide BMS)
- if you experience an increased **sensitivity of the skin to the sun** with symptoms of sunburn (such as redness, itching, swelling, blistering) occurring more quickly than normal
- if you are **going to have an operation** (surgery) or **be given anaesthetics**

The hydrochlorothiazide contained in this medicine could produce a positive result in an anti-doping test.

**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.

Diuretic agents such as the hydrochlorothiazide contained in Irbesartan Hydrochlorothiazide BMS may have an effect on other medicines. Preparations containing lithium should not be taken with Irbesartan Hydrochlorothiazide BMS without close supervision by your doctor.

**You may need to have blood checks if you take:**
- potassium supplements
- salt substitutes containing potassium
- potassium sparing medicines or other diuretics (water tablets)
- some laxatives
- medicines for the treatment of gout
- therapeutic vitamin D supplements
- medicines to control heart rhythm
- medicines for diabetes (oral agents or insulins)

It is also important to tell your doctor if you are taking other medicines to reduce your blood pressure, steroids, medicines to treat cancer, pain killers or arthritis medicines.

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

Due to the hydrochlorothiazide contained in Irbesartan Hydrochlorothiazide BMS, if you drink alcohol while on treatment with this medicine, you may have an increased feeling of dizziness on standing up, specially when getting up from a sitting position.

**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 Hydrochlorothiazide 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 Hydrochlorothiazide BMS. Irbesartan Hydrochlorothiazide 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 Hydrochlorothiazide 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 Hydrochlorothiazide 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 Hydrochlorothiazide BMS**
**Irbesartan Hydrochlorothiazide 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 HYDROCHLOROTHIAZIDE BMS

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

**Dosage**
The usual dose of Irbesartan Hydrochlorothiazide BMS is one tablet a day. Irbesartan Hydrochlorothiazide BMS will usually be prescribed by your doctor when your previous treatment did not reduce your blood pressure enough. Your doctor will instruct you how to switch from the previous treatment to Irbesartan Hydrochlorothiazide BMS.

**Method of administration**
Irbesartan Hydrochlorothiazide BMS is for **oral use**. Swallow the tablets with a sufficient amount of fluid (e.g. one glass of water). You can take Irbesartan Hydrochlorothiazide 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 Hydrochlorothiazide BMS until your doctor tells you otherwise.

The maximal blood pressure lowering effect should be reached 6-8 weeks after beginning treatment.

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

**Children should not take Irbesartan Hydrochlorothiazide BMS**
Irbesartan Hydrochlorothiazide 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 Hydrochlorothiazide 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 Hydrochlorothiazide BMS can cause side effects, although not everybody gets them.
Some of these effects may be serious and may require medical attention.

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 the above symptoms or get short of breath,** stop taking Irbesartan Hydrochlorothiazide BMS and contact your doctor immediately.

Side effects reported in clinical studies for patients treated with Irbesartan Hydrochlorothiazide BMS were:

**Common side effects** *(affect 1 to 10 users in 100)*
- nausea/vomiting
- abnormal urination
- fatigue
- dizziness (including when getting up from a lying or sitting position)
- blood tests may show raised levels of an enzyme that measures the muscle and heart function (creatine kinase) or raised levels of substances that measure kidney function (blood urea nitrogen, creatinine).

**If any of these side effects causes you problems**, talk to your doctor.

**Uncommon side effects** *(affect 1 to 10 users in 1,000)*
- diarrhoea
- low blood pressure
- fainting
- heart rate increased
- flushing
- swelling
- sexual dysfunction (problems with sexual performance)
- blood tests may show lowered levels of potassium and sodium in your blood.

**If any of these side effects causes you problems**, talk to your doctor.

**Side effects reported since the launch of Irbesartan Hydrochlorothiazide BMS**
The frequency of these effects is not known. These undesirable effects are: headache, ringing in the ears, cough, taste disturbance, indigestion, pain in joints and muscles, liver function abnormal and impaired kidney function, increased level of potassium in your blood and allergic reactions such as rash, hives, swelling of the face, lips, mouth, tongue or throat.

As for any combination of two active substances, side effects associated with each individual component cannot be excluded.
**Side effects associated with irbesartan alone**
In addition to the side effects listed above, chest pain has also been reported.
**Side effects associated with hydrochlorothiazide alone**
Loss of appetite; stomach irritation; stomach cramps; constipation; jaundice (yellowing of the skin and/or whites of the eyes); inflammation of the pancreas characterised by severe upper stomach pain, often with nausea and vomiting; sleep disorders; depression; blurred vision; lack of white blood cells, which can result in frequent infections, fever; decrease in the number of platelets (a blood cell essential for the clotting of the blood), decreased number of red blood cells (anaemia) characterised by tiredness, headaches, being short of breath when exercising, dizziness and looking pale; kidney disease; lung problems including pneumonia or build-up of fluid in the lungs; increased sensitivity of the skin to the sun; inflammation of blood vessels; a skin disease characterized by the peeling of the skin all over the body; cutaneous lupus erythematosus, which is identified by a rash that may appear

on the face, neck, and scalp; allergic reactions; weakness and muscle spasm; altered heart rate; reduced blood pressure after a change in body position; swelling of the salivary glands; high sugar levels in the blood; sugar in the urine; increases in some kinds of blood fat; high uric acid levels in the blood, which may cause gout.

It is known that side effects associated with hydrochlorothiazide may increase with higher doses of hydrochlorothiazide.

**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 HYDROCHLOROTHIAZIDE BMS

Keep out of the reach and sight of children.

Do not use Irbesartan Hydrochlorothiazide 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.

Store in the original package in order to protect from moisture.

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 Hydrochlorothiazide BMS contains**

- The active substances are irbesartan and hydrochlorothiazide. Each film-coated tablet of Irbesartan Hydrochlorothiazide BMS 300 mg/25 mg contains 300 mg irbesartan and 25 mg hydrochlorothiazide.
- The other ingredients are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hypromellose, silicon dioxide, magnesium stearate, titanium dioxide, macrogol 3350, red, yellow and black ferric oxides, pregelatinized starch, carnauba wax.

**What Irbesartan Hydrochlorothiazide BMS looks like and contents of the pack**
Irbesartan Hydrochlorothiazide BMS 300 mg/25 mg film-coated tablets are pink, biconvex, oval-shaped, with a heart debossed on one side and the number 2788 engraved on the other side.

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Not all pack sizes may be marketed.

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