Public Assessment Report

Decentralised Procedure

Irbesartan/Hydrochlorothiazide 150mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg Tablets

Procedure No: UK/H/3697/001-3/DC

UK Licence No: PL 34771/0088-90

Macleods Pharma UK Limited
Lay summary

On 01 May 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations to Macleods Pharma UK Limited for the medicinal products Irbesartan/Hydrochlorothiazide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg tablets (PL 34771/0088-90; UK/H/3697/001-3/DC). These products are prescription-only medicines (POM) used to treat high blood pressure, when treatment with irbesartan or hydrochlorothiazide alone does not provide adequate control of blood pressure.

Irbesartan/Hydrochlorothiazide tablets are a combination products consisting 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 tablets work together to lower blood pressure further than if either was given alone.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Irbesartan/Hydrochlorothiazide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg tablets; outweigh the risks and Marketing Authorisations were granted.
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Module 1

Information about the initial procedure

| Product Names | UK/H/3697/001/DC: Irbesartan/Hydrochlorothiazide 150 mg/12.5 mg tablets  
UK/H/3697/002/DC: Irbesartan/Hydrochlorothiazide 300 mg/12.5 mg tablets  
UK/H/3697/003/DC: Irbesartan/Hydrochlorothiazide 300 mg/25 mg tablets |
<table>
<thead>
<tr>
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<th></th>
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<tbody>
<tr>
<td>Type of Applications</td>
<td>Generic, Article 10(1)</td>
</tr>
<tr>
<td>Active Substance</td>
<td>Irbesartan/Hydrochlorothiazide</td>
</tr>
<tr>
<td>Form</td>
<td>Film-coated tablets</td>
</tr>
<tr>
<td>Strengths</td>
<td>150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg</td>
</tr>
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</table>
| MA Holder | Macleods Pharma UK Limited  
Golden Gate Lodge,  
Crewe Hall, Crewe, Cheshire,  
CW1 6UL,  
United Kingdom |
| Reference Member State (RMS) | UK |
| Concerned Member States (CMS) | Germany, Spain and Italy |
| Procedure Numbers | UK/H/3697/001-3/DC |
| Timetable | Day 210 – 20 March 2012 |
Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Irbesartan/Hydrochlorothiazide 150 mg/12.5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 150 mg of Irbesartan & 12.5 mg of Hydrochlorothiazide

Excipient: contains Lactose monohydrate

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet

Peach coloured, oval, film coated tablets debossed with “ML 34” on one side and plain on 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 Tablets 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 Tablets 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 Tablets 300 mg/12.5 mg may be administered in patients insufficiently controlled by irbesartan 300 mg or by Irbesartan/Hydrochlorothiazide Tablets 150 mg/12.5 mg
- Irbesartan/Hydrochlorothiazide Tablets 300 mg/25 mg may be administered in patients insufficiently controlled by Irbesartan/Hydrochlorothiazide Tablets 300 mg/25 mg.

Doses higher than 300 mg irbesartan/25 mg hydrochlorothiazide once daily are not recommended.

When necessary, Irbesartan/Hydrochlorothiazide Tablets may be administered with another antihypertensive medicinal product (see section 4.5).

Renal impairment: due to the hydrochlorothiazide component, Irbesartan/Hydrochlorothiazide Tablets 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 $\geq 30$ ml/min (see sections 4.3 and 4.4).

Hepatic impairment: Irbesartan/Hydrochlorothiazide Tablets 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 Tablets is necessary in patients with mild to moderate hepatic impairment (see section 4.3).

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

Paediatric patients: Irbesartan/Hydrochlorothiazide Tablets 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: the combination of irbesartan/hydrochlorothiazide 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 Tablets.

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 Tablets, a similar effect should be anticipated.

Renal impairment and kidney transplantation: when Irbesartan/Hydrochlorothiazide Tablets is used in patients with impaired renal function, a periodic monitoring of potassium, creatinine and uric acid serum levels is recommended.

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 \( \geq 30 \) ml/min. However, in patients with mild to moderate renal impairment (creatinine clearance \( \geq 30 \) 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 Tablets 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 Tablets 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 Tablets, 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 Tablets 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 Tablets (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 hypomagnesaemia.

Lithium: the combination of lithium and Irbesartan/Hydrochlorothiazide Tablets 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 readministration 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 Tablets 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 Tablets. Therefore, the combination of lithium and Irbesartan/Hydrochlorothiazide Tablets 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, carbeneoxolone, 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 Tablets 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. Irbesartan/Hydrochlorothiazide Tablets should be taken at least one hour before or four hours after these medications;
**Corticosteroids, ACTH:** electrolyte depletion, particularly hypokalaemia, may be increased;

**Digitalis glycosides:** thiazide induced hypokalaemia or hypomagnesaemia 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 Fertility, Pregnancy and lactation

**Pregnancy:**

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

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

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

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

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

**Hydrochlorothiazide:** There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia. Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or
preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Cases of neonatal thrombocytopenia, or foetal or neonatal jaundice have been reported with maternal thiazide therapy. Since Irbesartan/Hydrochlorothiazide Tablets 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:**
Angiotensin II Receptor Antagonists (AIIRAs): Because no information is available regarding the use of Irbesartan/Hydrochlorothiazide of Macleods during breastfeeding, Irbesartan/Hydrochlorothiazide of Macleods is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Hydrochlorothiazide: Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of Irbesartan/Hydrochlorothiazide of Macleods during breast feeding is not recommended. If Irbesartan/Hydrochlorothiazide of Macleods is used during breast feeding, doses should be kept as low as possible.

**Fertility:**
The combination of irbesartan and hydrochlorothiazide has not been evaluated in definitive studies of fertility.

Irbesartan had no adverse effects on fertility or mating in male or female rats at about 5 times that found in humans receiving the maximum recommended dose of 300 mg/day (see section 5.3). Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex exposed to doses of up to 100 and 4 mg/kg respectively (see section 5.3).

**4.7 Effects on ability to drive and use machines**
No studies on the effects on the ability to drive and use machines have been performed. Based on its pharmacodynamic properties, Irbesartan/Hydrochlorothiazide Tablets 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:
Among 898 hypertensive patients who received various doses of irbesartan/hydrochlorothiazide (range: 37.5 mg/6.25 mg to 300 mg/25 mg) in placebo-controlled trials, 29.5% of the patients experienced adverse reactions. The most commonly reported ADRs were dizziness (5.6%), fatigue (4.9%), nausea/vomiting (1.8%), and abnormal urination (1.4%). In addition, increases in blood urea nitrogen (BUN) (2.3%), creatine kinase (1.7%) and creatinine (1.1%) were also commonly observed in the trials.

Table 1 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled trials.
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*

<table>
<thead>
<tr>
<th>Investigations:</th>
<th>Common:</th>
<th>Uncommon:</th>
<th>Not known:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigations:</strong></td>
<td>increases in blood urea nitrogen (BUN), creatinine and creatine kinase</td>
<td>decreases in serum potassium and sodium</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac disorders:</strong></td>
<td>syncope, hypotension, tachycardia, oedema</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nervous system disorders:</strong></td>
<td>dizziness</td>
<td>orthostatic dizziness</td>
<td>headache</td>
</tr>
<tr>
<td><strong>Ear and labyrinth disorders:</strong></td>
<td>tinnitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders:</strong></td>
<td>cough</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders:</strong></td>
<td>nausea/vomiting</td>
<td>diarrhoea</td>
<td>dyspepsia, dysgeusia</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders:</strong></td>
<td>abnormal urination</td>
<td>impaired renal function including isolated cases of renal failure in patients at risk (see section 4.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders:</strong></td>
<td>swelling extremity</td>
<td>arthralgia, myalgia</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders:</strong></td>
<td>hyperkalaemia</td>
<td></td>
<td></td>
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<tr>
<td><strong>Vascular disorders:</strong></td>
<td>flushing</td>
<td></td>
<td></td>
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<tr>
<td><strong>General disorders and administration site conditions:</strong></td>
<td>fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Immune system disorders:</strong></td>
<td>cases of hypersensitivity reactions such as angioedema, rash, urticaria</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders:</strong></td>
<td>hepatitis, abnormal liver function</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reproductive system and breast disorders:</strong></td>
<td>sexual dysfunction, libido changes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 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 Tablets. Tables 2 and 3 below detail the adverse reactions reported with the individual components of Irbesartan/Hydrochlorothiazide Tablets.

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 Tablets. 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/Hydrochlorothiazide Tablets 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\textsubscript{1} subtype) antagonist. It is expected to block all actions of angiotensin-II mediated by the AT\textsubscript{1} receptor, regardless of the source or route of synthesis of angiotensin-II. The selective antagonism of the angiotensin-II (AT\textsubscript{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 Tablets 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 Tablets 150 mg/12.5 mg and Irbesartan/Hydrochlorothiazide Tablets 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 Tablets, 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 Tablets, 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 Tablets 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 Tablets, the absolute oral bioavailability is 60-80% and 50-80% for irbesartan and hydrochlorothiazide, respectively. Food does not affect the bioavailability of Irbesartan/Hydrochlorothiazide Tablets. 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 $C_{\text{max}}$ values were also somewhat greater in elderly subjects ($\geq 65$ 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.

Irbesartan had no adverse effects on fertility or mating of male or female rats at oral doses = 650 mg/kg/day, the highest dose providing a systemic exposure to irbesartan (AUC_0-24 hour, bound plus unbound) about 5 times that found in humans receiving the maximum recommended dose of 300 mg/day.

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.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet core:
- Carboxymethylcellulose Calcium (ECG-505)
- Colloidal Silicon Dioxide (Aerosil 200)
- Povidone (PVP K29/32)
- Sodium Starch Glycolate Type A (Glycolys)
- Talc
- Magnesium Stearate

Film coating:
- Hypromellose 15 cp (E464)
- Lactose Monohydrate
- Titanium Dioxide (E171)
- Polyethylene Glycol 3000
- Iron Oxide Red & Yellow (E172)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months
6.4 **Special precautions for storage**
This medicinal product does not require any special storage conditions.

6.5 **Nature and contents of container**
Blister pack: PVdC coated white opaque PVC/PE film/Aluminium foil in a carton box.

Pack size: 28’s

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**
Macleods Pharma UK Limited
Golden Gate Lodge,
Crewe Hall, Crewe, Cheshire,
CW1 6UL,
United Kingdom

8 **MARKETING AUTHORISATION NUMBER(S)**
PL34771/0088

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
01/05/2012

10 **DATE OF REVISION OF THE TEXT**
01/05/2012
1 **NAME OF THE MEDICINAL PRODUCT**
Irbesartan/Hydrochlorothiazide 300 mg/12.5 mg Tablets

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each film-coated tablet contains 300 mg of Irbesartan & 12.5 mg of Hydrochlorothiazide

Excipient: contains Lactose monohydrate

For a full list of excipients, see Section 6.1.

3 **PHARMACEUTICAL FORM**
Film-coated tablet

Peach coloured, oval, film coated tablets debossed with “ML 33” on one side and plain on 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 Tablets 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 Tablets 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 Tablets 300 mg/12.5 mg may be administered in patients insufficiently controlled by irbesartan 300 mg or by Irbesartan/Hydrochlorothiazide Tablets 150 mg/12.5 mg
- Irbesartan/Hydrochlorothiazide Tablets 300 mg/25 mg may be administered in patients insufficiently controlled by Irbesartan/Hydrochlorothiazide Tablets 300 mg/25 mg.

Doses higher than 300 mg irbesartan/25 mg hydrochlorothiazide once daily are not recommended.

When necessary, Irbesartan/Hydrochlorothiazide Tablets may be administered with another antihypertensive medicinal product (see section 4.5).

**Renal impairment:** due to the hydrochlorothiazide component, Irbesartan/Hydrochlorothiazide Tablets 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 \( \geq 30 \text{ ml/min} \) (see sections 4.3 and 4.4).

**Hepatic impairment:** Irbesartan/Hydrochlorothiazide Tablets 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 Tablets is necessary in patients with mild to moderate hepatic impairment (see section 4.3).

**Elderly patients:** no dosage adjustment of Irbesartan/Hydrochlorothiazide Tablets is necessary in elderly patients.

**Paediatric patients:** Irbesartan/Hydrochlorothiazide Tablets 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:** the combination of irbesartan/hydrochlorothiazide 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 Tablets.

**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 Tablets, a similar effect should be anticipated.

**Renal impairment and kidney transplantation:** when Irbesartan/Hydrochlorothiazide Tablets is used in patients with impaired renal function, a periodic monitoring of potassium, creatinine and uric acid serum levels is recommended.

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 $\geq 30$ ml/min. However, in patients with mild to moderate renal impairment (creatinine clearance $\geq 30$ 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 Tablets 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 Tablets 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 Tablets, 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 Tablets 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 Tablets (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 hypercalcemia 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 hypomagnesaemia.

Lithium: the combination of lithium and Irbesartan/Hydrochlorothiazide Tablets 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 readministration 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 Tablets 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 Tablets. Therefore, the combination of lithium and Irbesartan/Hydrochlorothiazide Tablets 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 poteniated by other medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbamazepine, 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 Tablets 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. Irbesartan/Hydrochlorothiazide Tablets should be taken at least one hour before or four hours after these medications;
Corticosteroids, ACTH: electrolyte depletion, particularly hypokalaemia, may be increased;

Digitalis glycosides: thiazide induced hypokalaemia or hypomagnesaemia 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 Fertility, Pregnancy and lactation

Pregnancy:

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

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

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

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

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

Hydrochlorothiazide: There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia. Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or
preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Cases of neonatal thrombocytopenia, or foetal or neonatal jaundice have been reported with maternal thiazide therapy. Since Irbesartan/Hydrochlorothiazide Tablets 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:
Angiotensin II Receptor Antagonists (AIIRAs): Because no information is available regarding the use of Irbesartan/Hydrochlorothiazide of Macleods during breastfeeding, Irbesartan/Hydrochlorothiazide of Macleods is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Hydrochlorothiazide: Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of Irbesartan/Hydrochlorothiazide of Macleods during breast feeding is not recommended. If Irbesartan/Hydrochlorothiazide of Macleods is used during breast feeding, doses should be kept as low as possible.

Fertility:
The combination of irbesartan and hydrochlorothiazide has not been evaluated in definitive studies of fertility.

Irbesartan had no adverse effects on fertility or mating in male or female rats at about 5 times that found in humans receiving the maximum recommended dose of 300 mg/day (see section 5.3).

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex exposed to doses of up to 100 and 4 mg/kg respectively (see section 5.3).

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. Based on its pharmacodynamic properties, Irbesartan/Hydrochlorothiazide Tablets 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:
Among 898 hypertensive patients who received various doses of irbesartan/hydrochlorothiazide (range: 37.5 mg/6.25 mg to 300 mg/25 mg) in placebo-controlled trials, 29.5% of the patients experienced adverse reactions. The most commonly reported ADRs were dizziness (5.6%), fatigue (4.9%), nausea/vomiting (1.8%), and abnormal urination (1.4%). In addition, increases in blood urea nitrogen (BUN) (2.3%), creatine kinase (1.7%) and creatinine (1.1%) were also commonly observed in the trials.

Table 1 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled trials.
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*

<table>
<thead>
<tr>
<th>Category</th>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigations:</strong></td>
<td>Common:</td>
<td>increases in blood urea nitrogen (BUN), creatinine and creatine kinase</td>
</tr>
<tr>
<td></td>
<td>Uncommon:</td>
<td>decreases in serum potassium and sodium</td>
</tr>
<tr>
<td><strong>Cardiac disorders:</strong></td>
<td>Uncommon:</td>
<td>syncope, hypotension, tachycardia, oedema</td>
</tr>
<tr>
<td><strong>Nervous system disorders:</strong></td>
<td>Common:</td>
<td>dizziness</td>
</tr>
<tr>
<td></td>
<td>Uncommon:</td>
<td>orthostatic dizziness</td>
</tr>
<tr>
<td></td>
<td>Not known:</td>
<td>headache</td>
</tr>
<tr>
<td><strong>Ear and labyrinth disorders:</strong></td>
<td>Not known:</td>
<td>tinnitus</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders:</strong></td>
<td>Not known:</td>
<td>cough</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders:</strong></td>
<td>Common:</td>
<td>nausea/vomiting</td>
</tr>
<tr>
<td></td>
<td>Uncommon:</td>
<td>diarrhoea</td>
</tr>
<tr>
<td></td>
<td>Not known:</td>
<td>dyspepsia, dysgeusia</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders:</strong></td>
<td>Common:</td>
<td>abnormal urination</td>
</tr>
<tr>
<td></td>
<td>Not known:</td>
<td>impaired renal function including isolated cases of renal failure in patients at risk (see section 4.4)</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders:</strong></td>
<td>Uncommon:</td>
<td>swelling extremity</td>
</tr>
<tr>
<td></td>
<td>Not known:</td>
<td>arthralgia, myalgia</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders:</strong></td>
<td>Not known:</td>
<td>hyperkalaemia</td>
</tr>
<tr>
<td><strong>Vascular disorders:</strong></td>
<td>Uncommon:</td>
<td>flushing</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions:</strong></td>
<td>Common:</td>
<td>fatigue</td>
</tr>
<tr>
<td><strong>Immune system disorders:</strong></td>
<td>Not known:</td>
<td>cases of hypersensitivity reactions such as angioedema, rash, urticaria</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders:</strong></td>
<td>Not known:</td>
<td>hepatitis, abnormal liver function</td>
</tr>
<tr>
<td><strong>Reproductive system and breast disorders:</strong></td>
<td>Uncommon:</td>
<td>sexual dysfunction, libido changes</td>
</tr>
</tbody>
</table>

* 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 Tablets. Tables 2 and 3 below detail the adverse reactions reported with the individual components of Irbesartan/Hydrochlorothiazide Tablets.

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

<table>
<thead>
<tr>
<th>Category</th>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions:</td>
<td>Uncommon:</td>
<td>chest pain</td>
</tr>
</tbody>
</table>
### Table 3: Adverse reactions (regardless of relationship to medicinal product) reported with the use of hydrochlorothiazide alone

<table>
<thead>
<tr>
<th>Category</th>
<th>Associated Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td>Not known: electrolyte imbalance (including hypokalaemia and hyponatraemia, see section 4.4), hyperuricaemia, glycosuria, hyperglycaemia, increases in cholesterol and triglycerides</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Not known: cardiac arrhythmias</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Not known: aplastic anaemia, bone marrow depression, neutropenia/agranulocytosis, haemolytic anaemia, leucopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Not known: vertigo, paraesthesia, light-headedness, restlessness</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Not known: transient blurred vision, xanthopsia</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Not known: respiratory distress (including pneumonitis and pulmonary oedema)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Not known: pancreatitis, anorexia, diarrhoea, constipation, gastric irritation, sialadenitis, loss of appetite</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Not known: interstitial nephritis, renal dysfunction</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Not known: anaphylactic reactions, toxic epidermal necrolysis, necrotizing angiitis (vasculitis, cutaneous vasculitis), cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, photosensitivity reactions, rash, urticaria</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Not known: weakness, muscle spasm</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Not known: postural hypotension</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Not known: fever</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Not known: jaundice (intrahepatic cholestatic jaundice)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Not known: depression, sleep disturbances</td>
</tr>
</tbody>
</table>

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 Tablets. 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 Tablets 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 (AT1 subtype) antagonist. It is expected to block all actions of angiotensin-II mediated by the AT1 receptor, regardless of the source or route of synthesis of angiotensin-II. The selective antagonism of the angiotensin-II (AT1) receptors results in increases in plasma renin levels and angiotensin-II levels, and a decrease in plasma aldosterone concentration. Serum potassium levels are not significantly affected by irbesartan alone at the recommended doses 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 Tablets 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 Tablets 150 mg/12.5 mg and Irbesartan/Hydrochlorothiazide Tablets 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 Tablets, 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 Tablets, 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 Tablets 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 Tablets, the absolute oral bioavailability is 60-80% and 50-80% for irbesartan and hydrochlorothiazide, respectively. Food does not affect the bioavailability of Irbesartan/Hydrochlorothiazide Tablets. 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 14C irbesartan, 80-85% of the circulating plasma radioactivity is attributable to unchanged irbesartan. Irbesartan is metabolised by the liver via glucuronide conjugation and oxidation. The major circulating metabolite is irbesartan glucuronide (approximately 6%). In vitro studies indicate that irbesartan is primarily oxidised by the cytochrome P450 enzyme CYP2C9; isoenzyme CYP3A4 has negligible effect. Irbesartan and its metabolites are eliminated by both biliary and renal pathways. After either oral or intravenous administration of 14C irbesartan, about 20% of the radioactivity is recovered in the urine, and the remainder in the faeces. Less than 2% of the dose is excreted in the urine as unchanged irbesartan. 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.

Irbesartan had no adverse effects on fertility or mating of male or female rats at oral doses = 650 mg/kg/day, the highest dose providing a systemic exposure to irbesartan (AUC_{0-24} hour, bound plus unbound) about 5 times that found in humans receiving the maximum recommended dose of 300 mg/day.

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.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet core:
Carboxymethylcellulose Calcium (ECG-505)
Colloidal Silicon Dioxide (Aerosil 200)
Povidone (PVP K29/32)
Sodium Starch Glycolate Type A (Glycolys)
Talc
Magnesium Stearate

Film coating:
Hypermellose 15 cp (E464)
Lactose Monohydrate
Titanium Dioxide (E171)
Polyethylene Glycol 3000
Iron Oxide Red & Yellow (E172)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Blister pack: PVdC coated white opaque PVC/PE film/Aluminium foil in a carton box.

Pack size: 28’s

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
Macleods Pharma UK Limited
Golden Gate Lodge,
Crewe Hall, Crewe, Cheshire,
CW1 6UL,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 34771/0089

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
01/05/2012

10 DATE OF REVISION OF THE TEXT
01/05/2012
1 NAME OF THE MEDICINAL PRODUCT
Irbesartan/Hydrochlorothiazide 300 mg/25 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 300 mg of Irbesartan & 25 mg of Hydrochlorothiazide

Excipient: contains Lactose monohydrate

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Pink coloured, oval, film coated tablets debossed with “ML 32” on one side and plain on 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 Tablets 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 Tablets 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 Tablets 300 mg/12.5 mg may be administered in patients insufficiently controlled by irbesartan 300 mg or by Irbesartan/Hydrochlorothiazide Tablets 150 mg/12.5 mg
• Irbesartan/Hydrochlorothiazide Tablets 300 mg/25 mg may be administered in patients insufficiently controlled by Irbesartan/Hydrochlorothiazide Tablets 300 mg/25 mg.

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

Renal impairment: due to the hydrochlorothiazide component, Irbesartan/Hydrochlorothiazide Tablets 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 Tablets 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 Tablets is necessary in patients with mild to moderate hepatic impairment (see section 4.3).

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

Paediatric patients: Irbesartan/Hydrochlorothiazide Tablets 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, hypercalcemia
- Severe hepatic impairment, biliary cirrhosis and cholestasis

4.4 Special warnings and precautions for use

Hypotension - Volume-depleted patients: the combination of irbesartan/hydrochlorothiazide 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 Tablets.

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 Tablets, a similar effect should be anticipated.

Renal impairment and kidney transplantation: when Irbesartan/Hydrochlorothiazide Tablets 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 Tablets in patients with a recent kidney transplantation. Irbesartan/Hydrochlorothiazide Tablets 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 Tablets 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 Tablets 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 Tablets, 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 Tablets 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 Tablets (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 hypomagnesaemia.

Lithium: the combination of lithium and Irbesartan/Hydrochlorothiazide Tablets 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 readministration 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 Tablets 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 Tablets. Therefore, the combination of lithium and Irbesartan/Hydrochlorothiazide Tablets 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 kalluretic 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 Tablets 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. Irbesartan/Hydrochlorothiazide Tablets should be taken at least one hour before or four hours after these medications;

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

Digitalis glycosides: thiazide induced hypokalaemia or hypomagnesaemia 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 Fertility, Pregnancy and lactation

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

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

Exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See section 5.3). Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

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

Hydrochlorothiazide: There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and
neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia. Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Cases of neonatal thrombocytopenia, or foetal or neonatal jaundice have been reported with maternal thiazide therapy. Since Irbesartan/Hydrochlorothiazide Tablets 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:**
Angiotensin II Receptor Antagonists (AIIRAs): Because no information is available regarding the use of Irbesartan/Hydrochlorothiazide of Macleods during breastfeeding, Irbesartan/Hydrochlorothiazide of Macleods is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Hydrochlorothiazide: Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of Irbesartan/Hydrochlorothiazide of Macleods during breast feeding is not recommended. If Irbesartan/Hydrochlorothiazide of Macleods is used during breast feeding, doses should be kept as low as possible.

**Fertility:**
The combination of irbesartan and hydrochlorothiazide has not been evaluated in definitive studies of fertility.

Irbesartan had no adverse effects on fertility or mating in male or female rats at about 5 times that found in humans receiving the maximum recommended dose of 300 mg/day (see section 5.3). Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex exposed to doses of up to 100 and 4 mg/kg respectively (see section 5.3).

**4.7 Effects on ability to drive and use machines**
No studies on the effects on the ability to drive and use machines have been performed. Based on its pharmacodynamic properties, Irbesartan/Hydrochlorothiazide Tablets 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:
Among 898 hypertensive patients who received various doses of irbesartan/hydrochlorothiazide (range: 37.5 mg/6.25 mg to 300 mg/25 mg) in placebo-controlled trials, 29.5% of the patients experienced adverse reactions. The most commonly reported ADRs were dizziness (5.6%), fatigue (4.9%), nausea/vomiting (1.8%), and abnormal urination (1.4%). In addition, increases in blood urea nitrogen (BUN) (2.3%), creatine kinase (1.7%) and creatinine (1.1%) were also commonly observed in the trials.

Table 1 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled trials.
The frequency of adverse reactions listed below is defined using the following convention:
very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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***

<table>
<thead>
<tr>
<th>Investigations:</th>
<th>Common:</th>
<th>increases in blood urea nitrogen (BUN), creatinine and creatine kinase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Uncommon:</td>
<td>decreases in serum potassium and sodium</td>
</tr>
<tr>
<td>Cardiac disorders:</td>
<td>Uncommon:</td>
<td>syncope, hypotension, tachycardia, oedema</td>
</tr>
<tr>
<td>Nervous system disorders:</td>
<td>Common:</td>
<td>dizziness</td>
</tr>
<tr>
<td></td>
<td>Uncommon:</td>
<td>orthostatic dizziness</td>
</tr>
<tr>
<td></td>
<td>Not known:</td>
<td>headache</td>
</tr>
<tr>
<td>Ear and labyrinth disorders:</td>
<td>Not known:</td>
<td>tinnitus</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders:</td>
<td>Not known:</td>
<td>cough</td>
</tr>
<tr>
<td>Gastrointestinal disorders:</td>
<td>Common:</td>
<td>nausea/vomiting</td>
</tr>
<tr>
<td></td>
<td>Uncommon:</td>
<td>diarrhoea</td>
</tr>
<tr>
<td></td>
<td>Not known:</td>
<td>dyspepsia, dysgeusia</td>
</tr>
<tr>
<td>Renal and urinary disorders:</td>
<td>Common:</td>
<td>abnormal urination</td>
</tr>
<tr>
<td></td>
<td>Not known:</td>
<td>impaired renal function including isolated cases of renal failure in patients at risk (see section 4.4)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders:</td>
<td>Uncommon:</td>
<td>swelling extremity</td>
</tr>
<tr>
<td></td>
<td>Not known:</td>
<td>arthralgia, myalgia</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders:</td>
<td>Not known:</td>
<td>hyperkalaemia</td>
</tr>
<tr>
<td>Vascular disorders:</td>
<td>Uncommon:</td>
<td>flushing</td>
</tr>
<tr>
<td>General disorders and administration site conditions:</td>
<td>Common:</td>
<td>fatigue</td>
</tr>
<tr>
<td>Immune system disorders:</td>
<td>Not known:</td>
<td>cases of hypersensitivity reactions such as angioedema, rash, urticaria</td>
</tr>
<tr>
<td>Hepatobiliary disorders:</td>
<td>Not known:</td>
<td>hepatitis, abnormal liver function</td>
</tr>
<tr>
<td>Reproductive system and breast disorders:</td>
<td>Uncommon:</td>
<td>sexual dysfunction, libido changes</td>
</tr>
</tbody>
</table>

* 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 Tablets. Tables 2 and 3 below detail the adverse reactions reported with the individual components of Irbesartan/Hydrochlorothiazide Tablets.

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

<table>
<thead>
<tr>
<th>General disorders and administration site conditions:</th>
<th>Uncommon:</th>
<th>chest pain</th>
</tr>
</thead>
</table>
### Table 3: Adverse reactions (regardless of relationship to medicinal product) reported with the use of hydrochlorothiazide alone

<table>
<thead>
<tr>
<th>Category</th>
<th>Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td>Electrolyte imbalance (including hypokalaemia and hyponatraemia, see section 4.4), hyperuricaemia, glycosuria, hyperglycaemia, increases in cholesterol and triglycerides</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Cardiac arrhythmias</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Aplastic anaemia, bone marrow, depression, neutropenia/agranulocytosis, haemolytic anaemia, leucopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Vertigo, paraesthesia, light-headedness, restlessness</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Transient blurred vision, xanthopsia</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Respiratory distress (including pneumonitis and pulmonary oedema)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Pancreatitis, anorexia, diarrhoea, constipation, gastric irritation, sialadenitis, loss of appetite</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Interstitial nephritis, renal dysfunction</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Anaphylactic reactions, toxic epidermal necrolysis, necrotizing angitis (vasculitis, cutaneous vasculitis), cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, photosensitivity reactions, rash, urticaria</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Weakness, muscle spasm</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Postural hypotension</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fever</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Jaundice (intrahepatic cholestatic jaundice)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Depression, sleep disturbances</td>
</tr>
</tbody>
</table>

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 Tablets. 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 Tablets 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\textsubscript{1} subtype) antagonist. It is expected to block all actions of angiotensin-II mediated by the AT\textsubscript{1} receptor, regardless of the source or route of synthesis of angiotensin-II. The selective antagonism of the angiotensin-II (AT\textsubscript{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 Tablets 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 Tablets 150 mg/12.5 mg and Irbesartan/Hydrochlorothiazide Tablets 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 Tablets, 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 Tablets, 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 Tablets as initial therapy for severe hypertension (defined as SeDBP $\geq 110$ 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 $\geq 65$ years of age, and just 2% were $\geq 75$ 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 Tablets, the absolute oral bioavailability is 60-80% and 50-80% for irbesartan and hydrochlorothiazide, respectively. Food does not affect the bioavailability of Irbesartan/Hydrochlorothiazide Tablets. 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 $C_{\text{max}}$ 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 \(^{14}\text{C}\) irbesartan, 80-85% of the circulating plasma radioactivity is attributable to unchanged irbesartan. Irbesartan is metabolised by the liver via glucuronide conjugation and oxidation. The major circulating metabolite is irbesartan glucuronide (approximately 6%). In vitro studies indicate that irbesartan is primarily oxidised by the cytochrome P450 enzyme CYP2C9; isoenzyme CYP3A4 has negligible effect. Irbesartan and its metabolites are eliminated by both biliary and renal pathways. After either oral or intravenous administration of \(^{14}\text{C}\) irbesartan, about 20% of the radioactivity is recovered in the urine, and the remainder in the faeces. Less than 2% of the dose is excreted in the urine as unchanged irbesartan. 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, hydroureret 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.

Irbesartan had no adverse effects on fertility or mating of male or female rats at oral doses = 650 mg/kg/day, the highest dose providing a systemic exposure to irbesartan (AUC₀-2₄ hour, bound plus unbound) about 5 times that found in humans receiving the maximum recommended dose of 300 mg/day.

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.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet core:
Carboxymethylcellulose Calcium (ECG-505)
Colloidal Silicon Dioxide (Aerosil 200)
Povidone (PVP K29/32)
Sodium Starch Glycolate Type A (Glycolys)
Talc
Magnesium Stearate

Film coating:
Hypromellose 15 cp (E464)
Lactose Monohydrate
Titanium Dioxide (E171)
Polyethylene Glycol 3000
Iron Oxide Red & Yellow & Black (E172)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Blister pack: PVdC coated white opaque PVC/PE film/Aluminium foil in a carton box.

Pack size: 28’s
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
Macleods Pharma UK Limited
Golden Gate Lodge,
Crewe Hall, Crewe, Cheshire,
CW1 6UL,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL34771/0090

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
01/05/2012

10 DATE OF REVISION OF THE TEXT
01/05/2012
Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER
Irbesartan/Hydrochlorothiazide 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.

1. WHAT IRBESARTAN/HYDROCHLOROTHIAZIDE TABLETS IS AND WHAT IT IS USED FOR
Irbesartan/Hydrochlorothiazide Tablets are 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 causes a lowering of blood pressure.
The two active ingredients in Irbesartan/Hydrochlorothiazide Tablets work together to lower blood pressure further than if one were given alone.
Irbesartan/Hydrochlorothiazide Tablets are 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 TABLETS
Do not take Irbesartan/Hydrochlorothiazide Tablets
- If you are allergic (hypersensitive) to Irbesartan or any of the other ingredients in Irbesartan/Hydrochlorothiazide Tablets.
- If you are allergic (hypersensitive) to any other sulfonamide-derived medicines.
- If you are more than 3 months pregnant. (It is also better to avoid Irbesartan/Hydrochlorothiazide Tablets 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 Tablets should not be given to children and adolescents (under 18 years).

Take special care with Irbesartan/Hydrochlorothiazide Tablets
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 had 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 Tablets 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 abnormality fast heart beat which may indicate an excessive effect of hydrochlorothiazide (contained in Irbesartan/Hydrochlorothiazide Tablets).
- 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 Tablets may have an effect on other medicines. Preparations containing lithium should not be taken with Irbesartan/Hydrochlorothiazide Tablets without close supervision by your doctor.

You may need to have blood tests 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 insulin)

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, antihistamines, or colestyramine or colestipol resins for lowering blood cholesterol.

Taking Irbesartan/Hydrochlorothiazide Tablets with food or a drink
Irbesartan/Hydrochlorothiazide Tablets can be taken with or without food.

Due to the hydrochlorothiazide contained in Irbesartan/Hydrochlorothiazide Tablets, if you drink alcohol while on treatment with this medicine, you may have an increased feeling of dizziness on standing up, especially 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 Tablets 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 Tablets. Irbesartan/Hydrochlorothiazide Tablets 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 Tablets is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed.

Driving and using machines
No studies on the effects on the ability to drive and use machines have been performed. Irbesartan/Hydrochlorothiazide Tablets is unlikely to affect your ability to drive or use machines. However, occasionally dizziness or weakness 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 Tablets
Irbesartan/Hydrochlorothiazide Tablets 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 TABLETS
Always take Irbesartan/Hydrochlorothiazide Tablets 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 Tablets is one tablet a day. Irbesartan/Hydrochlorothiazide Tablets 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 Tablets.

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

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

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

Children should not take Irbesartan/Hydrochlorothiazide Tablets
Irbesartan/Hydrochlorothiazide Tablets should not be given to children under 10 years of age. If a child swallows some tablets, contact your doctor immediately.

If you forgot to take Irbesartan/Hydrochlorothiazide Tablets
If you accidentally miss a daily dose, just take the next dose as normal. Do not take a double dose to make up for 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 Tablets can cause side effects, although not everyone 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 localized 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 a short of breath, stop taking Irbesartan/Hydrochlorothiazide Tablets and contact your doctor immediately.

Side effects reported in clinical studies for patients treated with Irbesartan/Hydrochlorothiazide Tablets 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 (creatinine 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)
- diarrhea
- low blood pressure
- tainting
- heat 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.

Some undesirable effects have been reported since the marketing of the correlation of Irbesartan and Hydrochlorothiazide but the frequency for them to occur is not known. These undesirable effects are: headache, ringing in the ears, cough, taste disturbances, 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. In patients taking Irbesartan alone, in addition to the side effects listed above, chest pain has also been reported.

Additional side effects associated with the use of hydrochlorothiazide alone are: loss of appetite, stomach irritation, stomach cramps, constipation; jaundice seen as yellowing of the skin and/or whites of the eyes; inflammation of the pancreas often caused 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 (anemia) 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 characterised by the peeling of the skin all over the body; cutaneous lupus erythematosus, which is identified by rash that may appear on the face, neck, and scalp; allergic reactions: weakness and muscle spasms, 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; increase 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 dose 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 TABLETS
Keep out of the reach and sight of children.
Do not use Irbesartan/Hydrochlorothiazide Tablets after the expiry date which is stated on the carton and on the blister after ExP. The expiry date refers to the last day of that month.
This medicinal product does not require any special storage conditions. Medicines should not be disposed of via wastewater or household waste.

Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Irbesartan/Hydrochlorothiazide Tablets contains
The active substances are Irbesartan and Hydrochlorothiazide. Each 38-mg coated tablet contains 150 mg irbesartan and 12.5 mg hydrochlorothiazide.

The other ingredients are:
- Cores: Carboxymethylcellulose Sodium (E467), Colloidal Silicon Dioxide (Aerosil 200), Povidone (PVP K30), Sodium Starch Glycolate Type A (E472), Tartrazine and Magnesium Stearate.
- Coating: Hydroxypropylmethyl cellulose 15 cp (E464), Lecithin monohydrate, Titanium Dioxide (E171) and Polyethylene glycol 3000, Iron oxide red (E172) & Iron oxide yellow (E172).

How do Irbesartan/Hydrochlorothiazide Tablets look like?
Irbesartan/Hydrochlorothiazide Tablets 150 mg/12.5 mg tablets are peach coloured, oval, film coated tablets dressed with "ML 54" on one side and pain on other side.

What is in a pack of Irbesartan/Hydrochlorothiazide Tablets?
Irbesartan/Hydrochlorothiazide Tablets 150 mg/12.5 mg tablets are supplied in blister packs containing 28 tablets.
PACKAGE LEAFLET: INFORMATION FOR THE USER

Irbesartan/Hydrochlorothiazide 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 Tablets are and what they are used for
2. Before you take Irbesartan/Hydrochlorothiazide Tablets
3. How to take Irbesartan/Hydrochlorothiazide Tablets
4. Possible side effects
5. How to store Irbesartan/Hydrochlorothiazide Tablets
6. Further information

1. WHAT IRBESARTAN/HYDROCHLOROTHIAZIDE TABLETS ARE AND WHAT THEY ARE USED FOR

Irbesartan/Hydrochlorothiazide Tablets 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 Tablets work together to lower blood pressure further than if either was given alone.
Irbesartan/Hydrochlorothiazide Tablets 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 TABLETS

Do not take Irbesartan/Hydrochlorothiazide Tablets
- If you are allergic (hypersensitive) to Irbesartan or any of the other ingredients of Irbesartan/Hydrochlorothiazide Tablets
- If you have diabetes or are at risk of developing diabetes
- 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 Tablets should not be given to children and adolescents (under 18 years).

Take special care with Irbesartan/Hydrochlorothiazide Tablets Tell your doctor if any of the following apply to you:
- If you get a severe sore throat or fever
- 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 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 Tablets 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 abdominal thirst, dry mouth, general weakness, drowsiness, muscle pain or cramps, nausea, vomiting, or an abnormal fast heart beat which may indicate an excessive loss of hydrochlorothiazide (contained in Irbesartan/Hydrochlorothiazide Tablets)
- 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 a urine-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 Tablets may affect your ability to drive or use machines. Having occasional dizziness or weakness 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 Tablets
Irbesartan/Hydrochlorothiazide Tablets 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 TABLETS
Always take Irbesartan/Hydrochlorothiazide Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure.

Dosage
The usual dose of Irbesartan/Hydrochlorothiazide Tablets is one tablet a day. Irbesartan/Hydrochlorothiazide Tablets 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 Tablets.

Method of administration
Irbesartan/Hydrochlorothiazide Tablets is for oral use. Swallow the tablets with a sufficient amount of fluid (e.g. one glass of water). You can take Irbesartan/Hydrochlorothiazide tablets 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 Tablets 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 Tablets than you should
If you accidentally take too many tablets, contact your doctor immediately.

Children should not take Irbesartan/Hydrochlorothiazide Tablets
Irbesartan/Hydrochlorothiazide Tablets 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 Tablets
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 Tablets 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 Tablets and contact your doctor immediately.

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

Common side effects (affect 1 to 10 users in 100)
• Local irritation
• 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 (creatinine 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.

Some undesirable effects have been reported since the marketing of the combination of irbesartan and hydrochlorothiazide but the frequency for them to occur is not known. These undesirable effects are: headaches, 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. In patients taking irbesartan alone, in addition to the side effects listed above, chest pain has also been reported.

Additional side effects associated with the use of hydrochlorothiazide alone are: loss of appetite, stomach irritation, stomach cramps, constipation; jaundice seen as 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 feeling pale; kidney disease; lung problems including pneumonia or build-up of fluid in the lungs; increased irritability of the skin to the sun; inflammation of blood vessels; a skin disease characterised by 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 muscular pains; altered heart rate; reduced blood pressure; alteration in body position; swelling of the salivary glands; high sugar levels in the blood; sugar in the urine; increases in some kinds of blood lipids and high uric acid levels in this 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 TABLETS

Keep out of the reach of and sight of children.

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

This medicinal product does not require any special storage conditions. Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Irbesartan/Hydrochlorothiazide Tablets contains
The active substances are irbesartan and hydrochlorothiazide. Each film-coated tablet contains 300 mg irbesartan and 12.5 mg hydrochlorothiazide.

The other ingredients are
• Carr: Carboxymethylcellulose Calcium (ECG-605), Colloidal silicon dioxide (Aerosil 200), Povidone (PVP K90/92), Sodium Starch Glycolate Type A (Glycocol), Talc & Magnesium Stearate.

Coating: Hypromellose 15 cp (E464), Lactose monohydrate, Titanium Dioxide (E171) & Polyethylene glycol 3000, Iron oxide red (E172) & Iron oxide yellow (E172).

What do Irbesartan/Hydrochlorothiazide Tablets look like?
Irbesartan/Hydrochlorothiazide Tablets 300 mg/12.5 mg tablets are peach coloured, oval, film coated tablets debossed with "ML 33" on one side and plain on other side.

What is in a pack of Irbesartan/Hydrochlorothiazide Tablets?
Irbesartan/Hydrochlorothiazide Tablets 300 mg/12.5 mg tablets are supplied in blister packs containing 26 tablets.

PAG 135001
Marketing Authorisation Holder
Macleods Pharma UK Limited,
Golden Gate Lodge, Crewe Hall,
Crewe, Cheshire,
CW1 6UL, United Kingdom

Manufacturer
Peakforton Pharmaceuticals Ltd.,
UKCrewe Hall, Crewe, Cheshire CW1 6UL, United Kingdom

This medicinal product is authorised in the Member States under the following names:

United Kingdom: Irbesartan/Hydrochlorothiazide Tablets 300 mg/12.5 mg tablets
Germany: Irbesartan/Hydrochlorothiazide Tablets 300 mg/12.5 mg film-coated tablets
Italy: Irbesartan/Hydrochlorothiazide Tablets 300 mg/12.5 mg film-coated tablets
Spain: Irbesartan/Hydrochlorothiazide Tablets 300 mg/12.5 mg comprimidos recubiertos con película

This leaflet was last revised in (03/2012)
In this leaflet:
1. What Ibesartan/Hydrochlorothiazide Tablets are and what they are used for
2. Before you take Ibesartan/Hydrochlorothiazide Tablets
3. How to take Ibesartan/Hydrochlorothiazide Tablets
4. Possible side effects
5. How to store Ibesartan/Hydrochlorothiazide Tablets
6. Further information

1. WHAT IBEFARTAN/HYDROCHLOROTHIAZIDE TABLETS IS AND WHAT IT IS USED FOR

Ibesartan/Hydrochlorothiazide Tablets are a combination of two active substances, Ibesartan and hydrochlorothiazide. Ibesartan 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. Ibesartan 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 Ibesartan/Hydrochlorothiazide Tablets work together to lower blood pressure further than if either was given alone. Ibesartan/Hydrochlorothiazide Tablets are used to treat blood pressure, when treatment with Ibesartan or hydrochlorothiazide alone did not provide adequate control of your blood pressure.

2. BEFORE YOU TAKE IBEFARTAN/HYDROCHLOROTHIAZIDE TABLETS

- If you are allergic (hypersensitive) to Ibesartan or any of the other ingredients of Ibesartan/Hydrochlorothiazide Tablets
- 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 Ibesartan/Hydrochlorothiazide Tablets in early pregnancy — see pregnancy section)
- If you have severe liver or kidney problems

3. HOW TO TAKE IBEFARTAN/HYDROCHLOROTHIAZIDE TABLETS

- If you have difficulty in producing urine
- If your doctor determines that you have persistently high calcium or low potassium levels in your blood

Ibesartan/Hydrochlorothiazide Tablets should not be given to children and adolescents (under 18 years).

Take special care with Ibesartan/Hydrochlorothiazide Tablets

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. Ibesartan/Hydrochlorothiazide Tablets 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 Ibesartan/Hydrochlorothiazide Tablets)
- 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 a urinalysis 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 Ibesartan/Hydrochlorothiazide Tablets may have an effect on other medicines. Preparations containing lithium should not be taken with Ibesartan/Hydrochlorothiazide Tablets 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 insulin)

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, arthritis medicines, or colestyramine and colestipol needed for lowering blood cholesterol.

Taking Ibesartan/Hydrochlorothiazide Tablets with food and drink

Ibesartan/Hydrochlorothiazide Tablets can be taken with or without food.

Due to the hydrochlorothiazide contained in Ibesartan/Hydrochlorothiazide Tablets, if you drink alcohol while on treatment with this medicine, you may have an increased feeling of dizziness on standing up, especially 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 Ibesartan/Hydrochlorothiazide Tablets before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Ibesartan/Hydrochlorothiazide Tablets. Ibesartan/Hydrochlorothiazide Tablets 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. Ibesartan/Hydrochlorothiazide Tablets is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed.

Driving and using machines

No studies on the effects on the ability to drive and use machines have been performed. Ibesartan/Hydrochlorothiazide Tablets is unlikely to affect your ability to drive or use machines. However, occasionally dizziness or weakness 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 Ibesartan/Hydrochlorothiazide Tablets

Ibesartan/Hydrochlorothiazide Tablets 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.

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Dosage
The usual dose of Irbesartan/Hydrochlorothiazide Tablets is one tablet a day. Irbesartan/Hydrochlorothiazide Tablets 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 Tablets.

Method of administration
Irbesartan/Hydrochlorothiazide Tablets are for oral use. Swallow the tablets with sufficient amount of fluid (e.g., one glass of water). You can take Irbesartan/Hydrochlorothiazide Tablets 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 Tablets 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 Tablets than you should
If you accidentally take too many tablets, contact your doctor immediately.

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

If you forget to take Irbesartan/Hydrochlorothiazide Tablets
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 Tablets can cause side effects, although not everybody gets them.

Some of these effects may be serious and may require medical attention.

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 (creatinine 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
• fainting
• heart rate increased
• 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. Some undesirable effects have been reported since the marketing of the combination of irbesartan and hydrochlorothiazide but the frequency for them to occur 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. In patients taking Irbesartan alone, in addition to the side effects listed above, chest pain has also been reported.

Additional side effects associated with the use of hydrochlorothiazide alone are: loss of appetite, stomach irritation, stomach cramps, constipation; jaundice seen as yellowing of the skin and/or whites of the eyes; inflammation of the pancreas characterized 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) characterized by tiredness, headaches, being short of breath when exercising; dizziness and looking pale; kidney disease; lung problems including pneumonia; 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 kind 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 TABLETS

Keep out of the reach and sight of children.

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

This medicinal product does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste.

Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Irbesartan/Hydrochlorothiazide Tablets contain
The active substances are Irbesartan and hydrochlorothiazide. Each film-coated tablet contains 300 mg irbesartan and 25 mg hydrochlorothiazide.

The other ingredients are:
- CMC Carboxymethylcellulose sodium (E407)
- Sodium Starch Glycolate Type A (E472)

Coating: Hydroxypropyl cellulose 15 cp (E464), Lactose monohydrate, Titanium Dioxide (E171) & Polyethylene glycol 3000, Iron oxide red (E172), Iron oxide yellow (E172) & Iron oxide black (E172).

What do Irbesartan/Hydrochlorothiazide Tablets look like?
Irbesartan/Hydrochlorothiazide Tablets 300 mg/25 mg tablets are pink coloured, oval, film coated tablets debossed with "ML 32" on one side and plain on other side.

What is in a pack of Irbesartan/Hydrochlorothiazide Tablets?
Irbesartan/Hydrochlorothiazide Tablets 300 mg/25 mg tablets are supplied in blister packs containing 28 tablets.

This leaflet was last revised in [9/2012]
Module 5
Scientific discussion during initial procedure

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Irbesartan/Hydrochlorothiazide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg tablets (PL 34771/0088-90; UK/H/3697/001-3/DC) could be approved. These products are prescription-only medicines (POM) indicated for the treatment of essential hypertension. Irbesartan/Hydrochlorothiazide tablets are indicated in adult patients whose blood pressure is not adequately controlled on irbesartan or hydrochlorothiazide alone.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Germany, Spain and Italy as Concerned Member States (CMS). These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of CoAprovel 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg film-coated tablets (Sanofi Pharma Bristol Myers Squibb SNC, France) which were authorised in the EEA via the Centralised Procedure on 15 October 1998.

Irbesartan/Hydrochlorothiazide tablets contain the active ingredients irbesartan and hydrochlorothiazide. Irbesartan is an Angiotensin II receptor antagonist. Angiotensin II receptor antagonists, also known as angiotensin receptor blockers (ARBs), AT₁-receptor antagonists or sartans, are a group of medicines which modulate the renin-angiotensin-aldosterone system. AT₁-receptor antagonists block the activation of angiotensin II AT₁-receptors. Blockade of AT₁-receptors directly causes vasodilatation, reduces secretion of vasopressin, reduces production and secretion of aldosterone, amongst other actions – the combined effect of which is reduction of blood pressure.

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts.

No new non-clinical data have been submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

One single-dose, bioequivalence study was submitted to support these applications, comparing the test product Irbesartan/Hydrochlorothiazide 300 mg/25 mg tablets (Macleods Pharma UK Limited, UK) with the reference product CoAprovel 300 mg/25 mg tablets (Sanofi Pharma Bristol Myers Squibb SNC, France). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical data were submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
The RMS and CMS considered that the applications could be approved at the end of procedure (Day 210) on 20 March 2012. After a subsequent national phase, licences were granted in the UK on 01 May 2012.

II. ABOUT THE PRODUCT

| Names of the products in the Reference Member State | UK/H/3697/001/DC: Irbesartan/Hydrochlorothiazide 150 mg/12.5 mg tablets  
UK/H/3697/002/DC: Irbesartan/Hydrochlorothiazide 300 mg/12.5 mg tablets  
UK/H/3697/003/DC: Irbesartan/Hydrochlorothiazide 300 mg/25 mg tablets |
| Names of the active substances (INN) | Irbesartan and hydrochlorothiazide |
| Pharmacotherapeutic classification (ATC code) | Angiotensin-II antagonists, combinations (ATC code: C09DA04) |
| Pharmaceutical form and strengths | Film-coated tablets  
150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg |
| Reference numbers for the Decentralised Procedure | UK/H/3697/001-3/DC |
| Reference Member State (RMS) | United Kingdom |
| Concerned Member States (CMS) | Spain, Germany and Italy |
| Marketing Authorisation Numbers | PL 34771/0088-90 |
| Name and address of the authorisation holder | Macleods Pharma UK Limited  
Golden Gate Lodge, Crewe Hall, Crewe, Cheshire, CW1 6UL, United Kingdom |

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE - IRBESARTAN

INN: Irbesartan
Chemical Name: 2-Butyl-3-[[2’-(1H-tetrazole-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]non-1-en-4-one
Molecular formula: C_{25}H_{28}N_{6}O
Structure:

![Chemical Structure of Irbesartan](image)

Relative molecular mass: 428.53
Appearance: A white to almost white crystalline powder
Solubility: Practically insoluble in water, sparingly soluble in methanol and slightly soluble in methylene chloride

Irbesartan is the subject of a European Pharmacopoeia monograph.

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

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the specification limits. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

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

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

**ACTIVE SUBSTANCE – HYDROCHLOROTHIAZIDE**

**INN:** Hydrochlorothiazide

**Chemical Name:** 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide;

**Molecular Formula:** C$_7$H$_8$ClN$_3$O$_4$S$_2$

**Structure:**

![Molecular Structure](image)

**Molecular weight:** 297.7 g/mol

**Appearance:** A white to almost white, crystalline powder.

**Solubility** Very slightly soluble in water, sparingly soluble in ethanol (96%), and soluble in acetone and dilute solutions of alkali hydroxides.

Hydrochlorothiazide is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance hydrochlorothiazide, except for the proposed packaging specifications and stability data are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

**DRUG PRODUCT**

**Other Ingredients**

Other ingredients consist of the pharmaceutical excipients in the tablet core, namely carboxymethylcellulose calcium (ECG-505), colloidal silicon dioxide (Aerosil 200), povidone (PVP K29/32), sodium starch glycolate Type A (Glycolys), talc, magnesium stearate, The tablet coatings are composed of hypromellose 15 cp (E464), lactose monohydrate, titanium dioxide (E171), polyethylene glycol 3000, iron oxide red (E172), iron oxide yellow (E172) and iron oxide black (E172, 300 mg/25 mg strength tablet) Appropriate justifications for the inclusion of each excipient have been provided.

All the excipients in the tablet core comply with their respective European Pharmacopoeia monographs. The tablet coatings are in compliance with their respective in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.
With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material other than calf rennet is used during the production of lactose monohydrate.

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

**Pharmaceutical Development**
The objective of the development programme was to formulate safe, efficacious, stable products that could be considered generic medicinal products of the reference products CoAprovel 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg film-coated tablets (Sanofi Pharma Bristol Myers Squibb SNC, France).

Suitable pharmaceutical development data have been provided for these applications.

Comparative *in-vitro* dissolution and impurity profiles have been provided for these products and their respective reference products.

**Manufacturing Process**
Satisfactory batch formulae have been provided for the manufacture of all strengths of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with pilot-scale batches and has shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation studies on the first 3 full-scale production batches.

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

**Container Closure System**
The tablets are packaged in polvinylidene chloride (PVdC) coated white opaque polyvinylchloride/polyethylene film/aluminium (PVC/PE film/Al) blisters. These are packed into cardboard cartons with Patient Information Leaflets in a pack size of 28 film-coated tablets.

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

**Stability**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. Based on the results, a shelf-life of 24 months has been proposed, with no special storage conditions.
Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study. The bioequivalence study is discussed in Section III.3, Clinical Aspects.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflets (PILs) and Labelling
The SmPCs, PILs and labelling are satisfactory from a pharmaceutical perspective.

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

MAA (Marketing Authorisation Application) Forms
All aspects of the MAA forms are satisfactory from a pharmaceutical perspective

Expert Report (Quality Overall Summary)
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of Marketing Authorisations is recommended.

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

NON-CLINICAL EXPERT REPORT (NON-CLINICAL)
The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

ENVIRONMENTAL RISK ASSESSMENT
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As these products are intended for generic substitution with products that are already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
The grant of Marketing Authorisations is recommended.
### III.3 CLINICAL ASPECTS

The clinical pharmacology of irbesartan and hydrochlorothiazide is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided or required for these applications.

#### Pharmacokinetics

In support of the applications, the Marketing Authorisation Holder submitted the following bioequivalence study:

A randomised, open label, single-dose, two-period, two-treatment, two-sequence, crossover study comparing the pharmacokinetics of the test product Irbesartan/Hydrochlorothiazide 300 mg/25 mg tablets (Macleods Pharma UK Limited, UK) and the reference product CoAprovel 300 mg/25 mg tablets (Sanofi Pharma Bristol Myers Squibb, France) in healthy adult male subjects under fasting conditions.

The subjects were given a single dose of either treatment with 240 ml of water after an overnight fast of at least 10-hours. Blood samples were collected before and up to 72 hours after each administration. The washout period between the treatment arms was 7 days. The pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters (geometric means, ratios and confidence intervals [CI]) of irbesartan</th>
<th>Irbesartan/HCTZ 300 mg /25 mg (Test)</th>
<th>CoAprovel 300 mg/25 mg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-t} (ng*hrs/mL)</td>
<td>19223.711</td>
<td>20713.848</td>
<td>92.81</td>
<td>86.99-99.01</td>
</tr>
<tr>
<td>AUC_{0-inf} (ng*hrs/mL)</td>
<td>20992.332</td>
<td>22218.609</td>
<td>94.48</td>
<td>88.83-100.49</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>4223.361</td>
<td>3978.324</td>
<td>106.16</td>
<td>101.20-111.36</td>
</tr>
</tbody>
</table>

**AUC_{0-inf}** area under the plasma concentration-time curve from time zero to infinity  
**AUC_{0-t}** area under the plasma concentration-time curve from time zero to t hours  
**C_{max}** maximum plasma concentration  
**SD** Standard deviation  
Ratios and 90% CI calculated from log-transformed data  
Irbesartan/HCTZ 300 mg /25 mg = Irbesartan/Hydrochlorothiazide 300 mg /25 mg

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters (geometric means, ratios and confidence intervals [CI]) of hydrochlorothiazide</th>
<th>Irbesartan/HCTZ 300 mg /25 mg (Test)</th>
<th>CoAprovel 300 mg /25 mg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-t} (ng*hrs/mL)</td>
<td>1326.938</td>
<td>1357.667</td>
<td>97.74</td>
<td>93.61-102.05</td>
</tr>
<tr>
<td>AUC_{0-inf} (ng*hrs/mL)</td>
<td>1442.083</td>
<td>1466.112</td>
<td>98.36</td>
<td>95.06-101.78</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>199.147</td>
<td>199.086</td>
<td>100.03</td>
<td>92.56-108.10</td>
</tr>
</tbody>
</table>

**AUC_{0-inf}** area under the plasma concentration-time curve from time zero to infinity  
**AUC_{0-t}** area under the plasma concentration-time curve from time zero to t hours  
**C_{max}** maximum plasma concentration  
**SD** Standard deviation  
Ratios and 90% CI calculated from log-transformed data  
Irbesartan/HCTZ 300 mg /25 mg = Irbesartan/Hydrochlorothiazide 300 mg /25 mg
The 90% confidence intervals of the test/reference ratio of geometric means for \( AUC_{0-t} \), \( AUC_{0-\inf} \) and \( C_{\text{max}} \) lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Note for Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1). Thus, the data support the claim that the test product Irbesartan/Hydrochlorothiazide 300 mg/25 mg tablets (Macleods Pharma UK Limited, UK) is bioequivalent to the reference product CoAprovel 300 mg /25 mg tablets (Sanofi Pharma Bristol Myers Squibb SNC, France) under fasting conditions.

As the 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg strength products meet the criteria specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1) for biowaiver, the results and conclusions from the bioequivalence study with the 300 mg/25 mg tablet strength can be extrapolated to the 150 mg/12.5 mg and, 300 mg/12.5 mg tablet strengths.

**EFFICACY**
The efficacy of irbesartan and hydrochlorothiazide is well-known. No new efficacy data have been submitted and none are required for applications of this type.

**SAFETY**
With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues arose during the bioequivalence study.

**PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN**
The Pharmacovigilance System, as described by Marketing Authorisation Holder, fulfils the requirements and provides adequate evidence that the Marketing Authorisation Holder has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

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

**SUMMARIES OF PRODUCT CHARACTERISTICS (SmPCs), PATIENT INFORMATION LEAFLETS (PILs) AND LABELLING**
The SmPCs, PILs and labelling are acceptable from a clinical perspective. The SmPCs are consistent with those for the originator products. The PILs are consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with current guidance.

**CLINICAL EXPERT REPORT (CLINICAL OVERVIEW)**
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**CONCLUSION**
The grant of Marketing Authorisations is recommended.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The quality characteristics of Irbesartan/Hydrochlorothiazide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of irbesartan and hydrochlorothiazide are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s 300 mg/25 mg strength tablet and the reference CoAprovel 300 mg /25 mg tablets (Sanofi Pharma Bristol Myers Squibb SNC, France). As the 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg strengths of the product meet the criteria specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1) for biowaiver, the results and conclusions from the bioequivalence study with the 300 mg/25 mg tablet strength can be extrapolated to the 150 mg/12.5 mg and 300 mg/12.5 mg tablet strengths.

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

PRODUCT LITERATURE
The SmPCs, PILs and labelling are satisfactory, and consistent with those for the reference products, where appropriate, along with current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with irbesartan and hydrochlorothiazide is considered to have demonstrated the therapeutic value of the products. The benefit/risk balance is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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