

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Irbesartan/Hydrochlorothiazide Teva 150 mg/12.5 mg film-coated tablets
Irbesartan/Hydrochlorothiazide Teva 300 mg/12.5 mg film-coated tablets
Irbesartan/Hydrochlorothiazide Teva 300 mg/25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Irbesartan/Hydrochlorothiazide Teva 150 mg/12.5 mg film-coated tablets

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

Irbesartan/Hydrochlorothiazide Teva 300 mg/12.5 mg film-coated tablets

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

Irbesartan/Hydrochlorothiazide Teva 300 mg/25 mg film-coated tablets

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Irbesartan/Hydrochlorothiazide Teva 150 mg/12.5 mg film-coated tablets

Light pink to pink, film-coated capsule shaped tablet. One side of the tablet debossed with the number "93". The other side of the tablet debossed with the number "7238".

Irbesartan/Hydrochlorothiazide Teva 300 mg/12.5 mg film-coated tablets

Light pink to pink, round film-coated tablet. One side of the tablet debossed with the number "2" and plain on the other side.

Irbesartan/Hydrochlorothiazide Teva 300 mg/25 mg film-coated tablets

Pink to dark pink, round film-coated tablet. One side of the tablet debossed with the number "3" and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension.

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

4.2 Posology and method of administration

Posology

Irbesartan/Hydrochlorothiazide Teva 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 Teva 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 Teva 300 mg/12.5 mg may be administered in patients insufficiently controlled by irbesartan 300 mg or by Irbesartan/Hydrochlorothiazide Teva 150 mg/12.5 mg.
- Irbesartan/Hydrochlorothiazide Teva 300 mg/25 mg may be administered in patients insufficiently controlled by Irbesartan/Hydrochlorothiazide Teva 300 mg/12.5 mg.

Doses higher than 300 mg irbesartan/25 mg hydrochlorothiazide once daily are not recommended. When necessary, Irbesartan/Hydrochlorothiazide Teva may be administered with another antihypertensive medicinal product (see sections 4.3, 4.4, 4.5 and 5.1).

Special Populations

Renal impairment

Due to the hydrochlorothiazide component, Irbesartan/Hydrochlorothiazide Teva 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 Teva 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 Teva is necessary in patients with mild to moderate hepatic impairment (see section 4.3).

Elderly population

No dosage adjustment of Irbesartan/Hydrochlorothiazide Teva is necessary in older people.

Paediatric population

Irbesartan/Hydrochlorothiazide Teva is not recommended for use in children and adolescents because the safety and efficacy have not been established. No data are available..

Method of Administration

For oral use.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1, or to other sulfonamide-derived substances (hydrochlorothiazide is a sulfonamide-derived substance)
- Second and third trimester 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
- The concomitant use of Irbesartan/Hydrochlorothiazide Teva with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment ($\text{GFR} < 60 \text{ ml/min/1.73 m}^2$) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

Hypotension - Volume-depleted patients

The combination of irbesartan and 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 Teva.

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 Teva, a similar effect should be anticipated.

Renal impairment and kidney transplantation

When Irbesartan/Hydrochlorothiazide Teva 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 Teva in patients with a recent kidney transplantation. Irbesartan/Hydrochlorothiazide Teva should not be used in patients with severe renal impairment (creatinine clearance < 30 ml/min) (see section 4.3). Thiazide diuretic-associated azotaemia 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.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Intestinal angioedema

Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including irbesartan (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, irbesartan/hydrochlorothiazide should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

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 Teva 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 Teva is not recommended.

Metabolic and endocrine effects

Thiazide therapy may impair glucose tolerance. Latent diabetes mellitus may become manifest during thiazide therapy. Irbesartan may induce hypoglycaemia, particularly in diabetic patients. In patients treated with insulin or antidiabetics an appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required when indicated (see section 4.5).

Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy; however at the 12.5 mg dose contained in the irbesartan and hydrochlorothiazide combination, 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 Teva 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 Teva (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 Teva 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, azotaemia, oliguria, or rarely acute renal failure (see section 4.5). As with any anti-hypertensive agent, excessive blood pressure decrease in patients with ischemic cardiopathy or ischemic cardiovascular disease could result in a myocardial infarction or stroke.

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics.

Cases of photosensitivity reactions have been reported with thiazides diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Pregnancy

Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative anti-

hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Choroidal effusion, acute Myopia and Secondary Acute Angle-Closure Glaucoma

Sulfonamide drugs or sulfonamide derivative drugs can cause an idiosyncratic reaction, resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. While hydrochlorothiazide is a sulfonamide, only isolated cases of acute angle-closure glaucoma have been reported so far with hydrochlorothiazide. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy (see section 4.8).

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Acute respiratory toxicity

Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Irbesartan/Hydrochlorothiazide Teva should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Excipient

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Other antihypertensive agents

The antihypertensive effect of Irbesartan/Hydrochlorothiazide Teva 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 and hydrochlorothiazide combinations. Therefore, the combination of lithium and Irbesartan/Hydrochlorothiazide Teva is not recommended (see section 4.4). If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Medicinal products affecting potassium

The potassium-depleting effect of hydrochlorothiazide is attenuated by the potassium-sparing effect of irbesartan. However, this effect of hydrochlorothiazide on serum potassium would be expected to be potentiated by other medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, penicillin G sodium). Conversely, based on the experience with the use of other medicinal products that blunt the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase serum potassium levels (e.g. heparin sodium) may lead to increases in serum potassium. Adequate monitoring of serum potassium in patients at risk is recommended (see section 4.4).

Medicinal products affected by serum potassium disturbances

Periodic monitoring of serum potassium is recommended when Irbesartan/Hydrochlorothiazide Teva 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.

Repaglinide

Irbesartan has the potential to inhibit OATP1B1. In a clinical study, it was reported that irbesartan increased the C_{max} and AUC of repaglinide (substrate of OATP1B1) by 1.8-fold and 1.3-fold, respectively, when administered 1 hour before repaglinide. In another study, no relevant pharmacokinetic interaction was reported, when the two drugs were co-administered. Therefore, dose adjustment of antidiabetic treatment such as repaglinide may be required (see section 4.4).

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

Potential 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 Teva 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;

Carbamazepine

Concomitant use of carbamazepine and hydrochlorothiazide has been associated with the risk of symptomatic hyponatraemia. Electrolytes should be monitored during concomitant use. If possible, another class of diuretics should be used;

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.

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

4.6 Fertility, pregnancy and lactation

Pregnancy

Angiotensin II Receptor Antagonists (AIIRAs)

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

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Antagonists

(AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to AIIRAs therapy during the second and third trimesters is known to induce human foetotoxicity (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.

Since Irbesartan/Hydrochlorothiazide Teva 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.

Breast-feeding

Angiotensin II Receptor Antagonists (AIIRAs)

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

It is unknown whether irbesartan or its metabolites are excreted in human milk.

Available pharmacodynamic/toxicological data in rats have shown excretion of irbesartan or its metabolites in milk (for details see 5.3).

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 Teva during breast feeding is not recommended. If Irbesartan/Hydrochlorothiazide Teva is used during breast feeding, doses should be kept as low as possible.

Fertility

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

4.7 Effects on ability to drive and use machines

Based on its pharmacodynamic properties, Irbesartan/Hydrochlorothiazide Teva is unlikely to affect the ability to drive and use machines. 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		
<i>Investigations:</i>	Common:	Increases in blood urea nitrogen (BUN), creatinine and creatine kinase
	Uncommon:	Decreases in serum potassium and sodium
<i>Cardiac disorders:</i>	Uncommon:	Syncope, hypotension, tachycardia, oedema
<i>Nervous system disorders:</i>	Common:	Dizziness
	Uncommon:	Orthostatic dizziness
	Not known:	Headache
<i>Ear and labyrinth disorders</i>	Not known:	Tinnitus
<i>Respiratory, thoracic and mediastinal disorders:</i>	Not known:	Cough
<i>Gastrointestinal disorders:</i>	Common:	Nausea/vomiting
	Uncommon:	Diarrhoea
	Not known:	Dyspepsia, dysgeusia
<i>Renal and urinary disorders:</i>	Common:	Abnormal urination
	Not known:	Impaired renal function including isolated cases of renal failure in patients at risk (see section 4.4)
<i>Musculoskeletal and connective tissue disorders:</i>	Uncommon:	Swelling extremity
	Not known:	Arthralgia, myalgia
<i>Metabolism and nutrition disorders:</i>	Not known:	Hyperkalaemia
<i>Vascular disorders:</i>	Uncommon:	Flushing
<i>General disorders and administration site conditions:</i>	Common:	Fatigue

<i>Immune system disorders:</i>	Not known:	Cases of hypersensitivity reactions such as angioedema, rash, urticaria
<i>Hepatobiliary disorders:</i>	Uncommon: Not known:	Jaundice Hepatitis, abnormal liver function
<i>Reproductive system and breast disorders:</i>	Uncommon:	Sexual dysfunction, libido changes

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

Table 2. Adverse reactions reported with the use of irbesartan alone		
<i>General disorders and administration site conditions:</i>	Uncommon:	Chest pain
<i>Blood and lymphatic system disorders:</i>	Not known:	Anaemia, thrombocytopenia
<i>Gastrointestinal disorders:</i>	Rare:	Intestinal angioedema
<i>Immune system disorders:</i>	Not known:	Anaphylactic reaction including anaphylactic shock
<i>Metabolism and nutrition disorders:</i>	Not known:	Hypoglycaemia

Table 3. Adverse reactions reported with the use of hydrochlorothiazide alone		
<i>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</i>	Not known	Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)
<i>Investigations:</i>	Not known:	Electrolyte imbalance (including hypokalaemia and hyponatraemia, see section 4.4), hyperuricaemia, glycosuria, hyperglycaemia, increases in cholesterol and triglycerides
<i>Cardiac disorders:</i>	Not known:	Cardiac arrhythmias
<i>Blood and lymphatic system disorders:</i>	Not known:	Aplastic anaemia, bone marrow depression, neutopenia/agranulocytosis, haemolytic anaemia, leucopenia, thrombocytopenia
<i>Nervous system disorders:</i>	Not known:	Vertigo, paraesthesia, light-headedness, restlessness
<i>Eye disorders:</i>	Not known:	Transient blurred vision, xanthopsia, choroidal effusion, acute myopia and secondary acute angle-closure glaucoma
<i>Respiratory, thoracic and mediastinal disorders:</i>	Very rare:	Acute respiratory distress syndrome (ARDS) (see section 4.4)
	Not known:	Respiratory distress (including pneumonitis and pulmonary oedema)

<i>Gastrointestinal disorders:</i>	Not known:	Pancreatitis, anorexia, diarrhoea, constipation, gastric irritation, sialadenitis, loss of appetite
<i>Renal and urinary disorders:</i>	Not known:	Interstitial nephritis, renal dysfunction
<i>Skin and subcutaneous tissue disorders:</i>	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
<i>Musculoskeletal and connective tissue disorders:</i>	Not known:	Weakness, muscle spasm
<i>Vascular disorders:</i>	Not known:	Postural hypotension
<i>General disorders and administration site conditions:</i>	Not known:	Fever
<i>Hepatobiliary disorders:</i>	Not known:	Jaundice (intrahepatic cholestatic jaundice)
<i>Psychiatric disorders:</i>	Not known:	Depression, sleep disturbances

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

Description of selected adverse reactions

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

No specific information is available on the treatment of overdose with irbesartan and hydrochlorothiazide combinations. 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, hyponatraemia, hypochloremia) 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: C09D A04

Mechanism of action

Irbesartan/Hydrochlorothiazide Teva 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 mmHg. 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 mmHg.

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 mmHg, 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 mmHg 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 mmHg. When measured by ambulatory blood pressure monitoring, the trough to peak effects of irbesartan/hydrochlorothiazide 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 150 mg/12.5 mg and irbesartan/hydrochlorothiazide 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 mmHg.

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 irbesartan/hydrochlorothiazide, 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, 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.

Clinical efficacy and safety

Efficacy and safety of irbesartan/hydrochlorothiazide as initial therapy for severe hypertension (defined as SeDBP \geq 110 mmHg) was evaluated in a multicentre, randomised, double-blind, active-controlled, 8-week, parallel-arm study. A total of 697 patients were randomised in a 2:1 ratio to either irbesartan/hydrochlorothiazide 150 mg/12.5 mg or to irbesartan 150 mg and systemically 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.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker. ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE- inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use ($\geq 50,000$ mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use ($\sim 25,000$ mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose ($\sim 100,000$ mg) (see also section 4.4).

5.2 Pharmacokinetic properties

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

Absorption

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

Distribution

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.

Linearity/non-linearity

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 older 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 older people. The mean plasma half-life of hydrochlorothiazide reportedly ranges from 5-15 hours.

Biotransformation

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.

Elimination

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.

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

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

Hydrochlorothiazide

Equivocal evidence for a genotoxic or carcinogenic effect was found in some experimental models.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Povidone

Pregelatinized starch (maize)

Poloxamer 188

Microcrystalline cellulose
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate

Film-coating for

150 mg/12.5 mg and 300 mg/12.5 mg strengths:

Hypromellose
Titanium Dioxide
Polyethylene Glycol 6000 (Macrogol)
Polyethylene Glycol 400 (Macrogol)
Iron Oxide Red
Iron Oxide Yellow
Iron Oxide Black

Film-coating for

300 mg/25 mg strength:

Hypromellose
Titanium Dioxide
Polyethylene Glycol 6000 (Macrogol)
Polyethylene Glycol 400 (Macrogol)
Iron Oxide Red
Indigotine (Indigo carmine aluminium lake FD&C blue #2)
Iron Oxide Black

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

White opaque PVC-PVdC – Aluminium blisters: Do not store above 30°C.

Aluminium – Aluminium blisters: This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

White opaque PVC-PVdC - Aluminium blisters or Aluminium – Aluminium blisters.

Pack sizes of 7, 14, 15, 20, 28, 30, 56, 60, 84, 90, 98 and 100 film-coated tablets in non-perforated blisters.

Pack size of 50x1 film coated tablet in unit dose blisters.

Pack size of 28 film-coated tablets in non-perforated calendar blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

Irbesartan/Hydrochlorothiazide Teva 150 mg/12.5 mg film-coated tablets
EU/1/09/583/001-024
EU/1/09/583/073
EU/1/09/583/076

Irbesartan/Hydrochlorothiazide Teva 300 mg/12.5 mg film-coated tablets
EU/1/09/583/025-048
EU/1/09/583/074
EU/1/09/583/077

Irbesartan/Hydrochlorothiazide Teva 300 mg/25 mg film-coated tablets
EU/1/09/583/049-072
EU/1/09/583/075
EU/1/09/583/078

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 November 2009
Date of latest renewal: 11 November 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the European Medicines Agency web site:
<http://www.ema.europa.eu/>

ANNEX II

- A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE
MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND
EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Teva Operations Poland Sp.z.o.o
ul. Mogilska 80
31-546 Kraków
Poland

Teva Pharmaceutical Works Private Limited Company
Pallagi út 13.
Debrecen H-4042
Hungary

Pharmachemie B.V.
Swensweg 5
2031 GA Haarlem
The Netherlands

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• Risk Management plan

Not applicable.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Irbesartan/Hydrochlorothiazide Teva 150 mg/12.5 mg film-coated tablets
irbesartan/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablets

7 film-coated tablets
14 film-coated tablets
15 film-coated tablets
20 film-coated tablets
28 film-coated tablets
30 film-coated tablets
56 film-coated tablets
60 film-coated tablets
84 film-coated tablets
90 film-coated tablets
98 film-coated tablets
100 film-coated tablets
50x1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

White opaque PVC-PVdC - Aluminium blisters: Do not store above 30°C.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/583/001-024
EU/1/09/583/073
EU/1/09/583/076

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Irbesartan/Hydrochlorothiazide Teva 150 mg/12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Irbesartan/Hydrochlorothiazide Teva 150 mg/12.5 mg film-coated tablets
irbesartan/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Teva B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

CALENDAR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Irbesartan/Hydrochlorothiazide Teva 150 mg/12.5 mg film-coated tablets
irbesartan/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Teva B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. OTHER

Monday Tuesday Wednesday Thursday Friday Saturday Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Irbesartan/Hydrochlorothiazide Teva 300 mg/12.5 mg film-coated tablets
irbesartan/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablets

7 film-coated tablets
14 film-coated tablets
15 film-coated tablets
20 film-coated tablets
28 film-coated tablets
30 film-coated tablets
56 film-coated tablets
60 film-coated tablets
84 film-coated tablets
90 film-coated tablets
98 film-coated tablets
100 film-coated tablets
50x1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

White opaque PVC-PVdC - Aluminium blisters: Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Teva B.V.
Swensweg 5
2031GA Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/583/025-048
EU/1/09/583/074
EU/1/09/583/077

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Irbesartan/Hydrochlorothiazide Teva 300 mg/12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Irbesartan/Hydrochlorothiazide Teva 300 mg/12.5 mg film-coated tablets
irbesartan/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Teva B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

CALENDAR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Irbesartan/Hydrochlorothiazide Teva 300 mg/12.5 mg film-coated tablets
irbesartan/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Teva B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. OTHER

Monday Tuesday Wednesday Thursday Friday Saturday Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Irbesartan/Hydrochlorothiazide Teva 300 mg/25 mg film-coated tablets
irbesartan/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablets

7 film-coated tablets
14 film-coated tablets
15 film-coated tablets
20 film-coated tablets
28 film-coated tablets
30 film-coated tablets
56 film-coated tablets
60 film-coated tablets
84 film-coated tablets
90 film-coated tablets
98 film-coated tablets
100 film-coated tablets
50x1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

White opaque PVC-PVdC - Aluminium blisters: Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Teva B.V.
Swensweg 5
2031GA Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/583/049-072
EU/1/09/583/075
EU/1/09/583/078

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Irbesartan/Hydrochlorothiazide Teva 300 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Irbesartan/Hydrochlorothiazide Teva 300 mg/25 mg film-coated tablets
irbesartan/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Teva B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

CALENDAR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Irbesartan/Hydrochlorothiazide Teva 300 mg/25 mg film-coated tablets
irbesartan/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Teva B.V.

3. EXPIRY DATE

EXP

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LOT

5. OTHER

Monday Tuesday Wednesday Thursday Friday Saturday Sunday

B. PACKAGE LEAFLET

Package leaflet: information for the patient

Irbesartan/Hydrochlorothiazide Teva 150 mg/12.5 mg film-coated tablets irbesartan / hydrochlorothiazide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Irbesartan/Hydrochlorothiazide Teva is and what it is used for
2. What you need to know before you take Irbesartan/Hydrochlorothiazide Teva
3. How to take Irbesartan/Hydrochlorothiazide Teva
4. Possible side effects
5. How to store Irbesartan/Hydrochlorothiazide Teva
6. Contents of the pack and other information

1. What Irbesartan/Hydrochlorothiazide Teva is and what it is used for

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

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

2. What you need to know before you take Irbesartan/Hydrochlorothiazide Teva

Do not take Irbesartan/Hydrochlorothiazide Teva

- if you are allergic to irbesartan or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to hydrochlorothiazole or to any other sulfonamide-derived medicines
- if you are more than 3 months pregnant (it is also better to avoid Irbesartan/Hydrochlorothiazide Teva 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.
- if you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren.

Warnings and precautions

Talk to your doctor before taking Irbesartan/Hydrochlorothiazide Teva and 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 transplantation
- if you suffer from heart problems
- if you suffer from liver problems
- if you suffer from diabetes
- if you develop **low blood sugar levels** (symptoms may include sweating, weakness, hunger, dizziness, trembling, headache, flushing or paleness, numbness, having a fast, pounding heart beat), particularly if you are being treated for 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)
- if you are taking any of the following medicines used to treat high blood pressure:
 - an ACE-inhibitor (for example enalapril, lisinopril, ramipril), in particular if you have diabetes-related kidney problems.
 - aliskiren
- if you have had skin cancer or if you develop an unexpected skin lesion during the treatment. Treatment with hydrochlorothiazide, particularly long term use with high doses, may increase the risk of some types of skin and lip cancer (non-melanoma skin cancer). Protect your skin from sun exposure and UV rays while taking Irbesartan/Hydrochlorothiazide Teva
- if you experienced breathing or lung problems (including inflammation or fluid in the lungs) following hydrochlorothiazide intake in the past. If you develop any severe shortness of breath or difficulty breathing after taking Irbesartan/Hydrochlorothiazide Teva, seek medical attention immediately.

Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.

See also information under the heading “Do not take Irbesartan/Hydrochlorothiazide Teva”.

Talk to your doctor if you experience abdominal pain, nausea, vomiting or diarrhoea after taking Irbesartan/Hydrochlorothiazide Teva. Your doctor will decide on further treatment. Do not stop taking Irbesartan/Hydrochlorothiazide Teva on your own.

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

You should also tell your doctor:

- if you are on a low-salt diet
- if you have signs such as abnormal thirst, dry mouth, general weakness, drowsiness, muscle pain or cramps, nausea, vomiting, or an abnormally fast heart beat which may indicate an excessive effect of hydrochlorothiazide (contained in Irbesartan/Hydrochlorothiazide Teva).
- 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
- if you have changes in your vision or pain in one or both of your eyes while taking Irbesartan/Hydrochlorothiazide Teva. This could be a sign of fluid accumulation in the vascular layer of the eye (choroidal effusion) or that you are developing glaucoma, increased pressure in your eye(s). You should discontinue Irbesartan/Hydrochlorothiazide Teva treatment and seek medical attention.

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

Children and adolescents

Irbesartan/Hydrochlorothiazide Teva should not be given to children and adolescents (under 18 years). If a child swallows some tablets, contact your doctor immediately.

Other medicines and Irbesartan/Hydrochlorothiazide Teva

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Your doctor may need to change your dose and/or to take other precautions:

If you are taking an ACE-inhibitor or aliskiren (see also information under the headings “Do not take Irbesartan/Hydrochlorothiazide Teva” and “Warnings and precautions”).

Diuretic agents such as the hydrochlorothiazide contained in Irbesartan/Hydrochlorothiazide Teva may have an effect on other medicines. Preparations containing lithium should not be taken with Irbesartan/Hydrochlorothiazide Teva 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 as repaglinide or insulins)
- carbamazepine (a medicine for the treatment of epilepsy).

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 resins for lowering blood cholesterol.

Irbesartan/Hydrochlorothiazide Teva with alcohol

Due to the hydrochlorothiazide contained in Irbesartan/Hydrochlorothiazide Teva, 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 Teva 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 Teva. Irbesartan/Hydrochlorothiazide Teva is not recommended during 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 Teva is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Driving and using machines

Irbesartan/Hydrochlorothiazide Teva is unlikely to affect your ability to drive or use machines. However, occasionally dizziness or weariness may occur during treatment of high blood pressure. If you experience these, talk to your doctor before attempting to drive or use machines.

Irbesartan/Hydrochlorothiazide Teva contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially ‘sodium-free’.

3. How to take Irbesartan/Hydrochlorothiazide Teva

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Dosage

The recommended dose of Irbesartan/Hydrochlorothiazide Teva is one or two tablets a day.

Irbesartan/Hydrochlorothiazide Teva will usually be prescribed by your doctor when your previous treatment for high blood pressure did not provide appropriate blood pressure reduction. Your doctor will instruct you how to switch from the previous treatment to Irbesartan/Hydrochlorothiazide Teva.

Method of administration

Irbesartan/Hydrochlorothiazide Teva is for **oral use**. Swallow the tablets with a sufficient amount of fluid (e.g. one glass of water). You can take Irbesartan/Hydrochlorothiazide Teva 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 Teva 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 Teva than you should

If you accidentally take too many tablets, contact your doctor immediately.

If you forget to take Irbesartan/Hydrochlorothiazide Teva

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 medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine 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 these symptoms or get short of breath**, stop taking Irbesartan/Hydrochlorothiazide Teva and contact your doctor immediately.

Side effects reported in clinical studies for patients treated with the combination of irbesartan and hydrochlorothiazide were:

Common side effects (may affect up to 1 in 10 people):

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

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

Uncommon side effects (may affect up to 1 in 100 people):

- 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. Undesirable effects where the frequency is not known 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. Uncommon cases of jaundice (yellowing of the skin and/or whites of the eyes) have also been reported.

As for any combination of two active substances, side effects associated with each individual component cannot be excluded.

Side effects associated with irbesartan alone:

In addition to the side effects listed above, chest pain, severe allergic reactions (anaphylactic shock), decreased number of red blood cells (anaemia – symptoms may include tiredness, headaches, being short of breath when exercising, dizziness and looking pale), decrease in the number of platelets (a blood cell essential for the clotting of the blood) and low blood sugar levels have also been reported.

Rare side effects (may affect up to 1 in 1,000 people): Intestinal angioedema: A swelling in the gut presenting with symptoms like abdominal pain, nausea, vomiting and diarrhoea.

Side effects associated with 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; decrease in vision or pain in your eyes due to high pressure (possible signs of fluid accumulation in the vascular layer of the eye (choroidal effusion) or acute angle-closure glaucoma); lack of white blood cells, which can result in frequent infections, fever; decrease in the number of platelets (a blood cell essential for the clotting of the blood), decreased number of red blood cells (anaemia) characterised by tiredness, headaches, being short of breath when exercising, dizziness and looking pale; kidney disease; lung problems including pneumonia or build-up of fluid in the lungs; increased sensitivity of the skin to the sun; inflammation of blood vessels; a skin disease characterized by the peeling of the skin all over the body; cutaneous lupus erythematosus, which is identified by a rash that may appear on the face, neck, and scalp; allergic reactions; weakness and muscle spasm; altered heart rate; reduced blood pressure after a change in body position; swelling of the salivary glands; high sugar levels in the blood; sugar in the urine; increases in some kinds of blood fat; high uric acid levels in the blood, which may cause gout.

Very rare side effects (may affect up to 1 in 10,000 people): Acute respiratory distress (signs include severe shortness of breath, fever, weakness, and confusion).

Frequency 'not known': Skin and lip cancer (Non-melanoma skin cancer)

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

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Irbesartan/Hydrochlorothiazide Teva

Keep this medicine out of the sight and reach of children.

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

For Irbesartan/Hydrochlorothiazide Teva packaged in white opaque PVC-PVdC – aluminium blisters: Do not store above 30°C.

For Irbesartan/Hydrochlorothiazide Teva packaged in aluminium – aluminium blisters: This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Irbesartan/Hydrochlorothiazide Teva contains

- The active ingredients are irbesartan and hydrochlorothiazide.
Each Irbesartan/Hydrochlorothiazide Teva 150 mg/12.5 mg film-coated tablet contains 150 mg irbesartan and 12.5 mg hydrochlorothiazide.
- The other ingredients are:
Tablet core: povidone, pregelatinized starch (maize), poloxamer 188, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica and magnesium stearate.
Tablet coating for 150 mg/12.5 mg strength: hypromellose, titanium dioxide, polyethylene glycol 6000 (macrogol), polyethylene glycol 400 (macrogol), iron oxide red, iron oxide yellow and iron oxide black.

What Irbesartan/Hydrochlorothiazide Teva looks like and contents of the pack

Irbesartan/Hydrochlorothiazide Teva 150 mg/12.5 mg film-coated tablets are light pink to pink, film coated capsule shaped tablets. One side of the tablet is debossed with the number “93” and the other side of the tablet is debossed with the number “7238”.

Irbesartan/Hydrochlorothiazide Teva is available in pack sizes of 7, 14, 15, 20, 28, 30, 56, 60, 84, 90, 98 and 100 film-coated tablets in non-perforated blisters; pack sizes of 50 x 1 film coated tablet in unit dose blisters and pack size of 28 film-coated tablets in non-perforated calendar blisters.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Teva B.V.
Swensweg 5
2031GA Haarlem
The Netherlands

Manufacturers:

Teva Operations Poland Sp.z.o.o
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Poland

Teva Pharmaceutical Works Private Limited Company
Pallagi út 13
Debrecen H-4042
Hungary

Pharmachemie B.V.
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2031 GA Haarlem
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For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

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Italia

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Sverige

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Latvija

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This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site:
<http://www.ema.europa.eu/>

Package leaflet: information for the patient

Irbesartan/Hydrochlorothiazide Teva 300 mg/12.5 mg film-coated tablets irbesartan / hydrochlorothiazide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Irbesartan/Hydrochlorothiazide Teva is and what it is used for
2. What you need to know before you take Irbesartan/Hydrochlorothiazide Teva
3. How to take Irbesartan/Hydrochlorothiazide Teva
4. Possible side effects
5. How to store Irbesartan/Hydrochlorothiazide Teva
6. Contents of the pack and other information

1. What Irbesartan/Hydrochlorothiazide Teva is and what it is used for

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

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

2. What you need to know before you take Irbesartan/Hydrochlorothiazide Teva

Do not take Irbesartan/Hydrochlorothiazide Teva

- if you are allergic to irbesartan or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to hydrochlorothiazole or to any other sulfonamide-derived medicines
- if you are more than 3 months pregnant (it is also better to avoid Irbesartan/Hydrochlorothiazide Teva 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.
- if you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren.

Warnings and precautions

Talk to your doctor before taking Irbesartan/Hydrochlorothiazide Teva and 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 transplantation
- if you suffer from heart problems
- if you suffer from liver problems
- if you suffer from diabetes
- if you develop **low blood sugar levels** (symptoms may include sweating, weakness, hunger, dizziness, trembling, headache, flushing or paleness, numbness, having a fast, pounding heart beat), particularly if you are being treated for 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)
- if you are taking any of the following medicines used to treat high blood pressure:
 - an ACE-inhibitor (for example enalapril, lisinopril, ramipril), in particular if you have diabetes-related kidney problems.
 - aliskiren
- if you have had skin cancer or if you develop an unexpected skin lesion during the treatment. Treatment with hydrochlorothiazide, particularly long term use with high doses, may increase the risk of some types of skin and lip cancer (non-melanoma skin cancer). Protect your skin from sun exposure and UV rays while taking Irbesartan/Hydrochlorothiazide Teva
- if you experienced breathing or lung problems (including inflammation or fluid in the lungs) following hydrochlorothiazide intake in the past. If you develop any severe shortness of breath or difficulty breathing after taking Irbesartan/Hydrochlorothiazide Teva, seek medical attention immediately.

Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.

See also information under the heading “Do not take Irbesartan/Hydrochlorothiazide Teva”.

Talk to your doctor if you experience abdominal pain, nausea, vomiting or diarrhoea after taking Irbesartan/Hydrochlorothiazide Teva. Your doctor will decide on further treatment. Do not stop taking Irbesartan/Hydrochlorothiazide Teva on your own.

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

You should also tell your doctor:

- if you are on a low-salt diet
- if you have signs such as abnormal thirst, dry mouth, general weakness, drowsiness, muscle pain or cramps, nausea, vomiting, or an abnormally fast heart beat which may indicate an excessive effect of hydrochlorothiazide (contained in Irbesartan/Hydrochlorothiazide Teva).
- 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
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The hydrochlorothiazide contained in this medicine could produce a positive result in an anti-doping test.

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Irbesartan/Hydrochlorothiazide Teva should not be given to children and adolescents (under 18 years). If a child swallows some tablets, contact your doctor immediately.

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Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Your doctor may need to change your dose and/or to take other precautions:

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Pregnancy and breast-feeding

Pregnancy

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The recommended dose of Irbesartan/Hydrochlorothiazide Teva is one tablet a day.

Irbesartan/Hydrochlorothiazide Teva will usually be prescribed by your doctor when your previous treatment for high blood pressure did not provide appropriate blood pressure reduction. Your doctor will instruct you how to switch from the previous treatment to Irbesartan/Hydrochlorothiazide Teva.

Method of administration

Irbesartan/Hydrochlorothiazide Teva is for oral use. Swallow the tablets with a sufficient amount of fluid (e.g. one glass of water). You can take Irbesartan/Hydrochlorothiazide Teva 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 Teva 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 Teva than you should

If you accidentally take too many tablets, contact your doctor immediately.

If you forget to take Irbesartan/Hydrochlorothiazide Teva

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 medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine 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 these symptoms or get short of breath**, stop taking Irbesartan/Hydrochlorothiazide Teva and contact your doctor immediately.

Side effects reported in clinical studies for patients treated with the combination of irbesartan and hydrochlorothiazide were:

Common side effects (may affect up to 1 in 10 people):

- 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 (may affect up to 1 in 100 people):

- 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. Undesirable effects where the frequency is not known 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. Uncommon cases of jaundice (yellowing of the skin and/or whites of the eyes) have also been reported.

As for any combination of two active substances, side effects associated with each individual component cannot be excluded.

Side effects associated with irbesartan alone:

In addition to the side effects listed above, chest pain, severe allergic reactions (anaphylactic shock), decreased number of red blood cells (anaemia – symptoms may include tiredness, headaches, being short of breath when exercising, dizziness and looking pale), decrease in the number of platelets (a blood cell essential for the clotting of the blood) and low blood sugar levels have also been reported.

Rare side effects (may affect up to 1 in 1,000 people): Intestinal angioedema: A swelling in the gut presenting with symptoms like abdominal pain, nausea, vomiting and diarrhoea.

Side effects associated with 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; decrease in vision or pain in your eyes due to high pressure (possible signs of fluid accumulation in the vascular layer of the eye (choroidal effusion) or acute angle-closure glaucoma); lack of white blood cells, which can result in frequent infections, fever; decrease in the number of platelets (a blood cell essential for the clotting of the blood), decreased number of red blood cells (anaemia) characterised by tiredness, headaches, being short of breath when exercising, dizziness and looking pale; kidney disease; lung problems including pneumonia or build-up of fluid in the lungs; increased sensitivity of the skin to the sun; inflammation of blood vessels; a skin disease characterized by the peeling of the skin all over the body; cutaneous lupus erythematosus, which is identified by a rash that may appear on the face, neck, and scalp; allergic reactions; weakness and muscle spasm; altered heart rate; reduced blood pressure after a change in body position; swelling of the salivary glands; high sugar levels in the blood; sugar in the urine; increases in some kinds of blood fat; high uric acid levels in the blood, which may cause gout.

Very rare side effects (may affect up to 1 in 10,000 people): Acute respiratory distress (signs include severe shortness of breath, fever, weakness, and confusion).

Frequency ‘not known’: Skin and lip cancer (Non-melanoma skin cancer)

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

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Irbesartan/Hydrochlorothiazide Teva

Keep this medicine out of the sight and reach of children.

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

For Irbesartan/Hydrochlorothiazide Teva packaged in white opaque PVC-PVdC – aluminium blisters: Do not store above 30°C.

For Irbesartan/Hydrochlorothiazide Teva packaged in aluminium – aluminium blisters: This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Irbesartan/Hydrochlorothiazide Teva contains

- The active ingredients are irbesartan and hydrochlorothiazide.
Each Irbesartan/Hydrochlorothiazide Teva 300 mg/12.5 mg film-coated tablet contains 300 mg irbesartan and 12.5 mg hydrochlorothiazide.
- The other ingredients are:
Tablet core: povidone, pregelatinized starch (maize), poloxamer 188, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica and magnesium stearate.
Tablet coating for 300 mg/12.5 mg strength: hypromellose, titanium dioxide, polyethylene glycol 6000 (macrogol), polyethylene glycol 400 (macrogol), iron oxide red, iron oxide yellow and iron oxide black.

What Irbesartan/Hydrochlorothiazide Teva looks like and contents of the pack

Irbesartan/Hydrochlorothiazide Teva 300 mg/12.5 mg film-coated tablets are light pink to pink, round film coated tablets. One side of the tablet debossed with the number “2” and plain on the other side.

Irbesartan/Hydrochlorothiazide Teva is available in pack sizes of 7, 14, 15, 20, 28, 30, 56, 60, 84, 90, 98 and 100 film-coated tablets in non-perforated blisters; pack sizes of 50 x 1 film coated tablet in unit dose blisters and pack size of 28 film-coated tablets in non-perforated calendar blisters.

Not all pack sizes may be marketed.

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This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site:
<http://www.ema.europa.eu/>

Package leaflet: information for the patient

Irbesartan/Hydrochlorothiazide Teva 300 mg/25 mg film-coated tablets irbesartan / hydrochlorothiazide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Irbesartan/Hydrochlorothiazide Teva is and what it is used for
2. What you need to know before you take Irbesartan/Hydrochlorothiazide Teva
3. How to take Irbesartan/Hydrochlorothiazide Teva
4. Possible side effects
5. How to store Irbesartan/Hydrochlorothiazide Teva
6. Contents of the pack and other information

1. What Irbesartan/Hydrochlorothiazide Teva is and what it is used for

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

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

2. What you need to know before you take Irbesartan/Hydrochlorothiazide Teva

Do not take Irbesartan/Hydrochlorothiazide Teva

- if you are allergic to irbesartan or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to hydrochlorothiazole or to any other sulfonamide-derived medicines
- if you are more than 3 months pregnant (it is also better to avoid Irbesartan/Hydrochlorothiazide Teva 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.
- if you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren.

Warnings and precautions

Talk to your doctor before taking Irbesartan/Hydrochlorothiazide Teva and 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 transplantation

- if you suffer from heart problems
- if you suffer from liver problems
- if you suffer from diabetes
- if you develop **low blood sugar levels** (symptoms may include sweating, weakness, hunger, dizziness, trembling, headache, flushing or paleness, numbness, having a fast, pounding heart beat), particularly if you are being treated for 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)
- if you are taking any of the following medicines used to treat high blood pressure:
 - an ACE-inhibitor (for example enalapril, lisinopril, ramipril), in particular if you have diabetes-related kidney problems.
 - aliskiren
- if you have had skin cancer or if you develop an unexpected skin lesion during the treatment. Treatment with hydrochlorothiazide, particularly long term use with high doses, may increase the risk of some types of skin and lip cancer (non-melanoma skin cancer). Protect your skin from sun exposure and UV rays while taking Irbesartan/Hydrochlorothiazide Teva
- if you experienced breathing or lung problems (including inflammation or fluid in the lungs) following hydrochlorothiazide intake in the past. If you develop any severe shortness of breath or difficulty breathing after taking Irbesartan/Hydrochlorothiazide Teva, seek medical attention immediately.

Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.

See also information under the heading “Do not take Irbesartan/Hydrochlorothiazide Teva”.

Talk to your doctor if you experience abdominal pain, nausea, vomiting or diarrhoea after taking Irbesartan/Hydrochlorothiazide Teva. Your doctor will decide on further treatment. Do not stop taking Irbesartan/Hydrochlorothiazide Teva on your own.

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

You should also tell your doctor:

- if you are on a low-salt diet
- if you have signs such as abnormal thirst, dry mouth, general weakness, drowsiness, muscle pain or cramps, nausea, vomiting, or an abnormally fast heart beat which may indicate an excessive effect of hydrochlorothiazide (contained in Irbesartan/Hydrochlorothiazide Teva).
- 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
- if you have changes in your vision or pain in one or both of your eyes while taking Irbesartan/Hydrochlorothiazide Teva. This could be a sign of fluid accumulation in the vascular layer of the eye (choroidal effusion) or that you are developing glaucoma, increased pressure in your eye(s). You should discontinue Irbesartan/Hydrochlorothiazide Teva treatment and seek medical attention.

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

Children and adolescents

Irbesartan/Hydrochlorothiazide Teva should not be given to children and adolescents (under 18 years). If a child swallows some tablets, contact your doctor immediately.

Other medicines and Irbesartan/Hydrochlorothiazide Teva

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Your doctor may need to change your dose and/or to take other precautions:

If you are taking an ACE-inhibitor or aliskiren (see also information under the headings “Do not take Irbesartan/Hydrochlorothiazide Teva” and “Warnings and precautions”).

Diuretic agents such as the hydrochlorothiazide contained in Irbesartan/Hydrochlorothiazide Teva may have an effect on other medicines. Preparations containing lithium should not be taken with Irbesartan/Hydrochlorothiazide Teva 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 as repaglinide or insulins)
- carbamazepine (a medicine for the treatment of epilepsy).

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 resins for lowering blood cholesterol.

Irbesartan/Hydrochlorothiazide Teva with alcohol

Due to the hydrochlorothiazide contained in Irbesartan/Hydrochlorothiazide Teva, 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 Teva 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 Teva. Irbesartan/Hydrochlorothiazide Teva is not recommended during 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 Teva is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Driving and using machines

Irbesartan/Hydrochlorothiazide Teva is unlikely to affect your ability to drive or use machines. However, occasionally dizziness or weariness may occur during treatment of high blood pressure. If you experience these, talk to your doctor before attempting to drive or use machines.

Irbesartan/Hydrochlorothiazide Teva contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially ‘sodium-free’.

3. How to take Irbesartan/Hydrochlorothiazide Teva

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Dosage

The recommended dose of Irbesartan/Hydrochlorothiazide Teva is one tablet a day.

Irbesartan/Hydrochlorothiazide Teva will usually be prescribed by your doctor when your previous treatment for high blood pressure did not provide appropriate blood pressure reduction. Your doctor will instruct you how to switch from the previous treatment to Irbesartan/Hydrochlorothiazide Teva.

Method of administration

Irbesartan/Hydrochlorothiazide Teva is for oral use. Swallow the tablets with a sufficient amount of fluid (e.g. one glass of water). You can take Irbesartan/Hydrochlorothiazide Teva 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 Teva 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 Teva than you should

If you accidentally take too many tablets, contact your doctor immediately.

If you forget to take Irbesartan/Hydrochlorothiazide Teva

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 medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine 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 these symptoms or get short of breath**, stop taking Irbesartan/Hydrochlorothiazide Teva and contact your doctor immediately.

Side effects reported in clinical studies for patients treated with the combination of irbesartan and hydrochlorothiazide were:

Common side effects (may affect up to 1 in 10 people):

- 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 (may affect up to 1 in 100 people):

- 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. Undesirable effects where the frequency is not known 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. Uncommon cases of jaundice (yellowing of the skin and/or whites of the eyes) have also been reported.

As for any combination of two active substances, side effects associated with each individual component cannot be excluded.

Side effects associated with irbesartan alone:

In addition to the side effects listed above, chest pain, severe allergic reactions (anaphylactic shock), decreased number of red blood cells (anaemia – symptoms may include tiredness, headaches, being short of breath when exercising, dizziness and looking pale), decrease in the number of platelets (a blood cell essential for the clotting of the blood) and low blood sugar levels have also been reported.

Rare side effects (may affect up to 1 in 1,000 people): Intestinal angioedema: A swelling in the gut presenting with symptoms like abdominal pain, nausea, vomiting and diarrhoea.

Side effects associated with 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; decrease in vision or pain in your eyes due to high pressure (possible signs of fluid accumulation in the vascular layer of the eye (choroidal effusion) or acute angle-closure glaucoma); lack of white blood cells, which can result in frequent infections, fever; decrease in the number of platelets (a blood cell essential for the clotting of the blood), decreased number of red blood cells (anaemia) characterised by tiredness, headaches, being short of breath when exercising, dizziness and looking pale; kidney disease; lung problems including pneumonia or build-up of fluid in the lungs; increased sensitivity of the skin to the sun; inflammation of blood vessels; a skin disease characterized by the peeling of the skin all over the body; cutaneous lupus erythematosus, which is identified by a rash that may appear on the face, neck, and scalp; allergic reactions; weakness and muscle spasm; altered heart rate; reduced blood pressure after a change in body position; swelling of the salivary glands; high sugar levels in the blood; sugar in the urine; increases in some kinds of blood fat; high uric acid levels in the blood, which may cause gout.

Very rare side effects (may affect up to 1 in 10,000 people): Acute respiratory distress (signs include severe shortness of breath, fever, weakness, and confusion).

Frequency ‘not known’: Skin and lip cancer (Non-melanoma skin cancer)

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

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Irbesartan/Hydrochlorothiazide Teva

Keep this medicine out of the sight and reach of children.

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

For Irbesartan/Hydrochlorothiazide Teva packaged in white opaque PVC-PVdC - aluminium blisters: Do not store above 30°C.

For Irbesartan/Hydrochlorothiazide Teva packaged in aluminium – aluminium blisters: This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Irbesartan/Hydrochlorothiazide Teva contains

- The active ingredients are irbesartan and hydrochlorothiazide.
Each Irbesartan/Hydrochlorothiazide Teva 300 mg/25 mg film-coated tablet contains 300 mg irbesartan and 25 mg hydrochlorothiazide.
- The other ingredients are:
Tablet core: povidone, pregelatinized starch (maize), poloxamer 188, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica and magnesium stearate.
Tablet coating for 300 mg/25 mg strength: hypromellose, titanium dioxide, polyethylene glycol 6000 (macrogol), polyethylene glycol 400 (macrogol), iron oxide red, Indigotine (Indigo carmine aluminium lake FD&C blue #2) and iron oxide black.

What Irbesartan/Hydrochlorothiazide Teva looks like and contents of the pack

Irbesartan/Hydrochlorothiazide Teva 300 mg/25 mg film-coated tablets are pink to dark pink, round film coated tablets. One side of the tablet debossed with the number "3" and plain on the other side.

Irbesartan/Hydrochlorothiazide Teva is available in pack sizes of 7, 14, 15, 20, 28, 30, 56, 60, 84, 90, 98 and 100 film-coated tablets in non-perforated blisters; pack sizes of 50 x 1 film coated tablet in unit dose blisters and pack size of 28 film-coated tablets in non-perforated calendar blisters.

Not all pack sizes may be marketed.

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Detailed information on this medicine is available on the European Medicines Agency (EMA) web site:
<http://www.ema.europa.eu/>