

PRODUCT INFORMATION**IRBESARTAN/HCT SANDOZ® Irbesartan/Hydrochlorothiazide
150/12.5MG, 300/12.5MG, 300/25MG
FILM-COATED TABLETS****NAME OF THE MEDICINE**

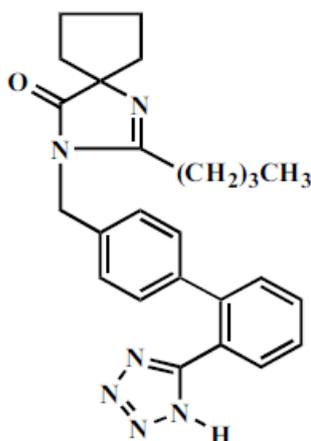
Generic name: Irbesartan/Hydrochlorothiazide.

Chemical Names:

Irbesartan: 2-butyl-3-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,3-diazaspiro[4,4]non-1-en-4-one

Hydrochlorothiazide: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

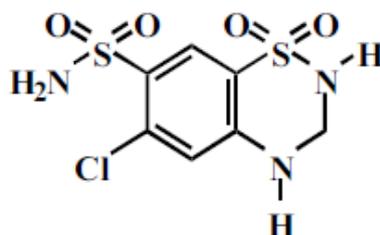
The chemical structure of irbesartan is:

**Irbesartan**

CAS number: CAS-1384-11-6

Empirical formula: C₂₅H₂₈N₆O MW: 428.5

The chemical structure of hydrochlorothiazide is:



Hydrochlorothiazide

CAS number: CAS-58-93-5

Empirical formula: C₇H₈ClN₃O₄S₂ MW: 297.73

DESCRIPTION

Irbesartan/HCT Sandoz 150mg/12.5mg tablets contain 150mg irbesartan and 12.5mg hydrochlorothiazide.

Irbesartan/HCT Sandoz 300mg/12.5mg tablets contain 300mg irbesartan and 12.5mg hydrochlorothiazide.

Irbesartan/HCT Sandoz 300mg/25mg tablets contain 300mg irbesartan and 25mg hydrochlorothiazide.

Irbesartan/HCT Sandoz (irbesartan/hydrochlorothiazide) is an oral antihypertensive agent combining a nonpeptide angiotensin II receptor (AT₁ subtype) antagonist, irbesartan and a thiazide diuretic, hydrochlorothiazide.

Irbesartan is a white to off-white crystalline powder. It is a relatively non-polar compound with a partition coefficient (octanol-water) of 10.1 at a pH of 7.4. Irbesartan is slightly soluble in alcohol and methylene chloride, and practically insoluble in water.

Hydrochlorothiazide is a white crystalline powder. It is slightly soluble in water but freely soluble in sodium hydroxide solution.

Irbesartan/HCT Sandoz 300mg/12.5mg and 150mg/12.5mg tablets contain the inactive ingredients: microcrystalline cellulose, lactose, croscarmellose sodium, colloidal anhydrous silica, hypromellose, magnesium stearate, hydroxypropylcellulose, macrogol 6000, titanium dioxide, talc, iron oxide red CI77491 and iron oxide yellow CI77492.

Irbesartan/HCT Sandoz 300mg/25mg tablets contain the inactive ingredients: microcrystalline cellulose, lactose, croscarmellose sodium, colloidal anhydrous silica, hypromellose, magnesium stearate, hydroxypropylcellulose, macrogol 6000, titanium dioxide, talc, iron oxide red CI77491 and iron oxide black CI77499.

PHARMACOLOGY

Pharmacodynamics

Irbesartan is a specific antagonist of angiotensin II receptors (AT₁ subtype). Angiotensin II is an important component of the renin-angiotensin system and is involved in the pathophysiology of hypertension and in sodium homeostasis. Irbesartan does not require metabolic activation for its activity.

Irbesartan blocks the potent vasoconstrictor and aldosterone-secreting effects of angiotensin II by selective antagonism of the angiotensin II (AT₁ subtype) receptors localized on vascular smooth muscle cells and in the adrenal cortex. It has no agonist activity at the AT₁ receptor and a much greater affinity (more than 8500-fold) for the AT₁ receptor than for the AT₂ receptor (a receptor that has not been shown to be associated with cardiovascular homeostasis).

Irbesartan does not inhibit enzymes involved in the renin-angiotensin system (i.e., renin, angiotensin converting enzyme [ACE]) or affect other hormone receptors or ion channels involved in the cardiovascular regulation of blood pressure and sodium homeostasis.

Hydrochlorothiazide is a benzothiadiazine (thiazide) diuretic with diuretic, natriuretic and antihypertensive effects. The mechanism of antihypertensive effect of thiazide diuretics, such as hydrochlorothiazide is not fully known. Thiazides affect the renal tubular mechanism of electrolyte reabsorption, increasing excretion of sodium and chloride in approximately equivalent amounts. Natriuresis causes a secondary loss of potassium and bicarbonate. Hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion, and decreases serum potassium. Coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics.

Pharmacokinetics

In a bioequivalence study comparing 300 mg /25 mg Irbesartan /Hydrochlorothiazide Sandoz tablets with the innovator's tablets, following an oral administration of single dose of Irbesartan / Hydrochlorothiazide Sandoz to healthy male subjects under fasting condition, a mean peak plasma concentration (C_{max}) of irbesartan of approximately 3784.9 ng/mL was achieved within approximately 1.25 hours (T_{max}) and a mean peak plasma concentration (C_{max}) of hydrochlorothiazide of approximately 190.55 ng/mL was achieved within approximately 1.75 hours (T_{max}).

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

Absorption:

The oral bioavailabilities of irbesartan and hydrochlorothiazide measured after administration of irbesartan/hydrochlorothiazide are similar to the bioavailabilities of irbesartan and hydrochlorothiazide administered as separate entities. The absolute oral bioavailability for irbesartan has previously been shown to be 60-80% whilst the absolute oral bioavailability for hydrochlorothiazide is documented as 50-80%.

Food does not affect the bioavailability of irbesartan/hydrochlorothiazide. Peak plasma concentrations occur 1.5-2 hours after oral administration for irbesartan and 1-2.5 hours for hydrochlorothiazide.

Distribution:

Irbesartan is 90% protein-bound in the plasma, and has negligible binding to cellular components of blood. The volume of distribution is 53-93 litres (0.72-1.24 Litres/Kg). Hydrochlorothiazide is 68% protein-bound in the plasma, and its apparent volume of distribution is 0.83 -1.141 Litres/Kg.

Metabolism:

In plasma, unchanged irbesartan accounts for more than 80% of the circulating radioactivity following oral or intravenous administration of ¹⁴C irbesartan. Irbesartan is metabolized by the liver via glucuronide conjugation and oxidation. The major circulating metabolite is irbesartan glucuronide (~6%). Irbesartan undergoes oxidation primarily by the cytochrome P450 isoenzyme *CYP2C9*; isoenzyme *CYP3A4* has negligible effect. It is not metabolized by, nor does it substantially induce or inhibit most isoenzymes commonly associated with medicine metabolism (i.e., *CYP1A1*, *CYP1A2*, *CYP2A6*, *CYP2B6*, *CYP2D6*, or *CYP2E1*). Irbesartan does not induce nor inhibit isoenzyme *CYP3A4*.

Hydrochlorothiazide is not metabolized.

Elimination:

Irbesartan and its metabolites are excreted by both biliary and renal routes. About 20% of the administered radioactivity after an oral or intravenous dose of ¹⁴C irbesartan is recovered in urine with the remainder in the faeces. Less than 2% of the dose is excreted in urine as unchanged irbesartan.

The terminal elimination half-life ($t_{1/2}$) of irbesartan from plasma is 11-15 hours. The total body clearance of intravenously administered irbesartan is 157-176mL/min, of which 3.0-3.5mL/min is renal clearance. Irbesartan exhibits linear pharmacokinetics over the therapeutic dose range. Steady-state plasma concentrations are attained within 3 days after initiation of a once-daily dosing regimen. Limited accumulation (<20%) is observed in plasma upon repeated once-daily dosing.

Hydrochlorothiazide is eliminated by the kidneys. The mean plasma half-life ($t_{1/2}$) of hydrochlorothiazide from plasma reportedly ranges from 5-15 hours.

Special Populations:

In male and female hypertensive subjects, higher (11-44%) plasma concentrations of irbesartan were observed in females than in males, although, following multiple dosing, males and females did not show differences in either accumulation or elimination half-life. No gender-specific differences in clinical effect have been observed.

In elderly (male and female) normotensive subjects (65-80 years) with clinically normal renal and hepatic function, the plasma AUC and peak plasma concentration (C_{max}) of irbesartan are approximately 20%-50% greater than those observed in younger subjects

(18-40 years). Regardless of age, the elimination half-life is comparable. No significant age-related differences in clinical effect have been observed. The area under the plasma concentration time curve (AUC) for hydrochlorothiazide was elevated in the elderly group following multiple dosing consistent with previously published data.

In black and white normotensive subjects, the plasma AUC and $t_{1/2}$ of irbesartan are approximately 20-25% greater in blacks than in whites; the peak plasma concentrations (C_{max}) of irbesartan are essentially equivalent.

In patients with renal impairment (regardless of degree) and in haemodialysis patients, the pharmacokinetics of irbesartan are not significantly altered. Irbesartan is not removed by haemodialysis. In patients with severe renal impairment (creatinine clearance <20mL/min), the elimination half-life of hydrochlorothiazide was reported to increase to 21 hours.

In patients with hepatic insufficiency due to mild to moderate cirrhosis, the pharmacokinetics of irbesartan is not significantly altered.

CLINICAL TRIALS

Based on data from placebo-controlled clinical trials, the following effects were noted. The blood pressure lowering effect of irbesartan in combination with hydrochlorothiazide was 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 blood pressure lowering effect of irbesartan/hydrochlorothiazide with dose-to-response addition of adjunctive therapy was maintained for over one year.

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

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

Once daily dosing with 150mg irbesartan and 12.5mg hydrochlorothiazide showed systolic/diastolic mean placebo-adjusted blood pressure reductions at trough (24 hours post-dosing) of 12.9/6.9mmHg. Peak effects occurred at 3-6 hours.

When assessed by ambulatory blood pressure monitoring, irbesartan/hydrochlorothiazide 150mg/12.5mg once daily produced consistent reduction in blood pressure over the 24 hours period with a mean 24-hour placebo-subtracted systolic/diastolic reductions of 15.8/10.0mmHg. The observed trough-to-peak effects were at least 68% of the corresponding placebo-subtracted peak diastolic and peak systolic responses.

In a clinical trial with patients not adequately controlled on 25mg hydrochlorothiazide alone after 4 weeks' treatment, the addition of irbesartan (with dose-to-response up-titration from 75mg to 150mg at 6 weeks) produced mean systolic/diastolic reductions at 12 weeks which were 11.1/7.2mmHg greater than hydrochlorothiazide alone.

Blood pressure was lowered to about the same extent in both standing and supine positions. Orthostatic effects were infrequent, but may be expected to occur in patients who develop intercurrent sodium and/or volume-depletion.

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.

The effectiveness of irbesartan/hydrochlorothiazide was not influenced by age, race, or gender. The overall antihypertensive response to the combination was similar for black and non black patients.

After withdrawal of irbesartan, blood pressure gradually returned toward baseline. Rebound hypertension was not observed with irbesartan or hydrochlorothiazide.

With hydrochlorothiazide, onset of diuresis occurred in 2 hours, and peak effect occurred at about 4 hours, while the action persisted for approximately 6-12 hours.

INDICATIONS

Irbesartan/HCT Sandoz is indicated for the treatment of hypertension. Treatment should not be initiated with this fixed-dose combination.

CONTRAINDICATIONS

Irbesartan/hydrochlorothiazide is contraindicated in patients who are hypersensitive to irbesartan, sulfonamide-derived medicines (e.g., thiazides), or to any other component of the irbesartan/hydrochlorothiazide formulation. In general, hypersensitivity reactions are more likely to occur in patients with a history of allergy or bronchial asthma.

Irbesartan/hydrochlorothiazide is contraindicated in patients who are anuric.

Refractory hypokalaemia, hypercalcaemia.

Severe hepatic impairment, biliary cirrhosis and cholestasis.

Do not co-administer irbesartan/hydrochlorothiazide with aliskiren-containing medicines in patients with diabetes or with moderate to severe renal impairment.

Do not co-administer irbesartan/hydrochlorothiazide with ACE inhibitors in patients with diabetic nephropathy.

Pregnancy (see **PRECAUTIONS**– Use in pregnancy).

PRECAUTIONS

Hypotension - Volume - Depleted Patients

Irbesartan/hydrochlorothiazide has been rarely associated with hypotension in hypertensive patients without other risk factors for hypotension. Symptomatic hypotension may be expected to occur in patients who have been sodium and/or volume depleted by vigorous diuretic therapy and/or dietary salt restriction, or vomiting and/or diarrhoea or haemodialysis. Volume and/or sodium depletion should be corrected before initiating therapy with irbesartan/hydrochlorothiazide. Thiazides may potentiate the action of other antihypertensive medicines (see **INTERACTIONS WITH OTHER MEDICINES**).

Renal Impairment

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function during therapy with irbesartan/hydrochlorothiazide may be anticipated in susceptible individuals. In patients whose renal function depends on the activity of the renin-angiotensin-aldosterone system (e.g., hypertensive patients with renal artery stenosis in one or both kidneys, or patients with severe congestive heart failure), treatment with medicines that affect this system has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. The possibility of a similar effect occurring with the use of an angiotensin II receptor antagonist, including irbesartan/hydrochlorothiazide cannot be excluded.

There is no experience with irbesartan/hydrochlorothiazide in patients with a recent renal transplant.

Irbesartan/hydrochlorothiazide is not recommended for patients with severe renal disease (creatinine clearance \leq 30mL/min) (see **CONTRAINDICATIONS** - anuric patients). Hydrochlorothiazide associated precipitation of azotemia may occur in patients with impaired renal function. As experience is limited in patients with a creatinine clearance >30 and < 60 mL/min, irbesartan/hydrochlorothiazide should be administered with caution to such patients.

When irbesartan/hydrochlorothiazide is used in patients with impaired renal function, a periodic monitoring of potassium, creatinine and uric acid serum levels is recommended.

Dual blockade of the Renin-Angiotensin-Aldosterone System (RAAS)

Dual blockade of the RAAS by combining irbesartan/hydrochlorothiazide with an ACE inhibitor or with aliskiren is not recommended since there are increased risk of hypotension, hyperkalemia, and changes in renal function. The use of irbesartan/hydrochlorothiazide in combination with aliskiren is contraindicated in patient with diabetes mellitus or renal impairment (see **CONTRAINDICATIONS**).

The use of irbesartan/hydrochlorothiazide in combination with aliskiren is contraindicated in patients with diabetes mellitus or with moderate to severe renal impairment.

The use of irbesartan/hydrochlorothiazide in combination with an ACE inhibitor is contraindicated in patients with diabetic nephropathy (see **CONTRAINDICATIONS** and **INTERACTIONS WITH OTHER MEDICINES**).

Renal Artery Stenosis

See comments under Renal Impairment above.

Primary Aldosteronism

Patients with primary aldosteronism generally will not respond to antihypertensive medicines acting through inhibition of the renin-angiotensin system. Therefore the use of irbesartan/hydrochlorothiazide is not recommended.

Postsympathectomy

The antihypertensive effects of thiazide diuretics may be increased in the postsympathectomy patient.

Impaired Hepatic Function

Irbesartan/hydrochlorothiazide should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations in fluid and electrolyte balance may precipitate hepatic coma.

Fluid and Electrolyte Imbalance

Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalemia, hyponatremia and hypochloremic alkalosis). Although hypokalemia may develop when thiazide diuretics are used alone, especially with higher doses, concurrent therapy with irbesartan reduces the frequency of diuretic-induced hypokalemia. 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 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.

Chloride deficit is generally mild and usually does not require treatment. Calcium excretion is decreased by thiazides which may cause intermittent and slight elevation of serum calcium. Marked hypercalcemia suggests the possibility of 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.

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.

Monitoring of laboratory parameters may be necessary in patients at risk of electrolyte imbalance.

Metabolic and Endocrine Effects

Hyperuricemia may occur, and an acute attack of gout may be precipitated in certain patients receiving thiazide therapy. Insulin requirements in diabetic patients may be increased and latent diabetes mellitus may become manifest during thiazide administration. Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy, however, minimal or no effects were reported at the 12.5mg hydrochlorothiazide dose contained in irbesartan/hydrochlorothiazide.

Monitoring of laboratory parameters may be necessary in patients at risk of metabolic disturbances.

Systemic Lupus Erythematosus

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

Cases of photosensitivity reactions have been reported with thiazide diuretics. If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If readministration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Acute Myopia and Secondary Acute Angle-Closure Glaucoma

Sulfonamide, or sulfonamide derivative, drugs can cause an idiosyncratic reaction, resulting in transient myopia and acute angle-closure glaucoma. While hydrochlorothiazide is a sulfonamide, isolated cases of acute angle-closure glaucoma without definite causal association 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.

Heart Failure

The safety of irbesartan in the presence of heart failure has not been fully defined. Sudden death has occurred in some studies of patients with heart failure, and although such deaths may have reflected the natural history of the underlying heart failure, caution is recommended when treating such patients with irbesartan.

Cardiac Arrhythmia

At this time, experience is limited with irbesartan in the treatment of patients with ventricular dysfunction or cardiac arrhythmias; caution is advised.

Effects on fertility

The effects of hydrochlorothiazide and the irbesartan/hydrochlorothiazide combination on fertility have not been evaluated in animal studies. However, with irbesartan alone, fertility and reproductive performance were not affected in studies of male and female rats at oral doses up to 650mg/kg/day (approximately 3 [male] and 8 [female] fold higher exposure based on AUC, than that of humans at the maximum recommended clinical dose of 300mg/day).

Carcinogenicity

The carcinogenic potential of irbesartan and hydrochlorothiazide in combination has not been evaluated in animal studies. However, the carcinogenic potential of irbesartan was assessed in two 104 week studies in mice and rats. No carcinogenic potential was observed in either species at doses of up to 500mg/kg/day (male rats) and 1000mg/kg/day (mice and female rats). The AUC based exposure levels were 3 - 6 fold higher in mice, 3 fold higher in male rats and 25 fold higher in female rats than that of humans at the maximum recommended clinical dose of 300mg/day. With hydrochlorothiazide two-year feeding studies in mice and rats uncovered no evidence of carcinogenic potential in female mice at doses up to approximately 600mg/kg/day, or in male and female rats at doses up to approximately 100mg/kg/day. The studies, however, uncovered equivocal evidence for hepatocarcinogenicity in male mice treated with hydrochlorothiazide at approximately 600mg/kg/day.

Genotoxicity

Irbesartan and the irbesartan/hydrochlorothiazide combination were not genotoxic in a series of assays for gene-mutagenic activity in bacterial and mammalian cells, and for clastogenic effects *in vitro* and *in vivo*. Hydrochlorothiazide alone was not genotoxic in a gene-mutation assay in bacterial cells, or in tests for clastogenic activity *in vitro* and *in vivo*. However, positive results were obtained in a mammalian cell assay for gene mutation (mouse lymphoma cell assay), and in two other tests (sister chromatid exchange assay in Chinese hamster ovary cells and nondisjunction assay in *Aspergillus nidulans*).

Use in Pregnancy (Category D)

Category D: Medicines which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These medicines may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Medicines that act directly on the renin-angiotensin system can cause foetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. When pregnancy is detected, irbesartan/hydrochlorothiazide should be discontinued as soon as possible.

The use of medicines that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy have been associated with foetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased foetal renal function; oligohydramnios in this setting has been associated with foetal limb contractures, craniofacial deformation and hypoplastic lung development. Prematurity, intrauterine growth retardation and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the medicine.

These adverse effects do not appear to have resulted from intrauterine medicine exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of irbesartan/hydrochlorothiazide as soon as possible.

As for any medicine that also acts directly on the RAAS, irbesartan/hydrochlorothiazide should not be used during pregnancy (see **CONTRAINDICATIONS**) or in women planning to become pregnant. Physicians prescribing any agents acting on the RAAS should warn women of childbearing potential about the potential risk of these agents during pregnancy.

Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria and hyperkalemia.

Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and foetus to unnecessary hazard, including foetal or neonatal jaundice, thrombocytopenia and possibly other adverse effects which have occurred in the adult.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or pre-eclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

No teratogenic effects were seen in rats given irbesartan and hydrochlorothiazide in combination at doses as high as 150/150mg/kg/day. When pregnant rats were treated with irbesartan alone from day 0 to day 20 of gestation, at doses of 50mg/kg/day and higher, transient effects (increased renal pelvic cavitation, hydroureter or subcutaneous oedema) were noted in full term rat fetuses but not in young animals necropsied after six weeks of age. In pregnant rabbits, at doses of 30mg/kg/day, maternal mortality, abortion and early foetal resorptions were noted. No teratogenic effects were observed in the rat or the rabbit.

Use in Lactation

Irbesartan is excreted in the milk of lactating rats. It is not known whether irbesartan or its metabolites are excreted in human milk. Hydrochlorothiazide is excreted in human breast milk. Thiazides in high doses causing intense diuresis can inhibit the milk

production. The use of irbesartan/hydrochlorothiazide during breastfeeding is not recommended.

Because of the potential risk to the infant, a decision should be made whether to discontinue breast feeding or to discontinue the medicine, taking into account the importance of irbesartan/hydrochlorothiazide to the therapy of the mother.

Use in the elderly

Among patients who received irbesartan/hydrochlorothiazide in clinical studies, no overall differences in efficacy or safety were observed between older patients (65 years or older) and younger patients.

Use in children

Safety and effectiveness in paediatric patients have not been established.

Effect on Laboratory Tests:

In premarketing controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of irbesartan/hydrochlorothiazide tablets.

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in 2.3 and 1.1 percent respectively, of patients with essential hypertension treated with irbesartan/hydrochlorothiazide alone. No patient discontinued taking irbesartan/hydrochlorothiazide due to increased BUN. One patient discontinued taking irbesartan/hydrochlorothiazide due to a minor increase in creatinine.

Haemoglobin: mean decreases of approximately 0.2g/dL occurred in patients treated with irbesartan/hydrochlorothiazide alone, but were rarely of clinical importance. This compared to a mean of 0.4g/dL in patients receiving placebo. No patients were discontinued due to anaemia.

Liver Function Tests: Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with irbesartan/hydrochlorothiazide alone, one patient was discontinued due to elevated liver enzymes.

Serum Electrolytes: In double-blind clinical trials of various doses of irbesartan and hydrochlorothiazide, the incidence of hypertensive patients who developed hypokalemia (serum potassium <3.5mmol/L) was 7.5% versus 6.0% for placebo; the incidence of hyperkalemia (serum potassium >5.7mmol/L) was < 1.0% versus 1.7% for placebo. No patient discontinued due to increases or decreases in serum potassium. Overall, the combination of irbesartan and hydrochlorothiazide had no effect on serum potassium. Higher doses of irbesartan ameliorated the hypokalemic response to hydrochlorothiazide. (see **PRECAUTIONS- Fluid and Electrolyte Imbalance**).

Driving/Operating Machinery

The effects of irbesartan/hydrochlorothiazide on the ability to drive motor vehicles or operate machinery have not been specifically studied, but based on its pharmacodynamic properties. Irbesartan/hydrochlorothiazide is unlikely to affect this

ability. When driving vehicles or operating machinery, it should be taken into account that occasionally dizziness may occur during treatment of hypertension.

INTERACTIONS WITH OTHER MEDICINES

Based on *in vitro* data, no interactions with irbesartan would be expected to occur with medicines whose metabolism is dependent upon cytochrome P450 isoenzymes *CYP1A1*, *CYP1A2*, *CYP2A6*, *CYP2B6*, *CYP2D6*, *CYP2E1* or *CYP3A4*. Irbesartan is primarily metabolized by *CYP2C9*, however, during clinical interaction studies, no significant pharmacokinetic and pharmacodynamic interactions were observed when irbesartan was co-administered with warfarin (a medicine metabolized by *CYP2C9*).

Irbesartan does not affect the pharmacokinetics of digoxin or simvastatin. The pharmacokinetics of irbesartan is not affected by coadministration with nifedipine or hydrochlorothiazide.

Based on experience with the use of other medicines that affect the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase kalaemia with irbesartan may lead to increases in serum potassium, sometimes severe, and requires close monitoring of serum potassium. Concurrent therapy with hydrochlorothiazide may reduce the frequency of this effect.

Alcohol, barbiturates or narcotics - Potentiation of thiazide diuretic - induced orthostatic hypotension may occur.

Antidiabetic medicines (oral agents and insulin) - Thiazides may elevate blood glucose levels thus, dosage adjustments of antidiabetic agents may be necessary.

Antigout medication - Dosage adjustments of antigout medication may be needed since hydrochlorothiazide may raise the blood level of uric acid. Co-administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol.

Cardiac glycosides (e.g., digoxin) and other antiarrhythmic medicines (e.g., sotalol) - Diuretic induced hypokalemia may accentuate cardiac arrhythmias.

Calcium salts - Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium or a calcium sparing medicine (e.g. Vitamin D therapy) is prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly.

Cholestyramine resin and colestipol HCl - May delay or decrease absorption of hydrochlorothiazide. Irbesartan/hydrochlorothiazide should be taken at least one hour before or four hours after these medications.

Lithium - Diuretic agents reduce the renal clearance of lithium and increase the risk of lithium toxicity. Increases in serum lithium concentrations and lithium toxicity have

been reported with concomitant use of irbesartan. Monitor lithium levels in patients receiving irbesartan and lithium.

Inhibitors of Endogenous Prostaglandin Synthesis (i.e., NSAIDs) - In some patients, these agents can reduce the effects of thiazide diuretics.

Other diuretics and antihypertensive medications - The thiazide component of irbesartan/hydrochlorothiazide may potentiate the actions of other antihypertensive medicines, especially ganglionic or peripheral adrenergic-blocking medicines. Hydrochlorothiazide may interact with diazoxide; blood glucose, serum uric acid levels and blood pressure should be monitored.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory medicines and thiazide diuretics - Concomitant use of a renin-angiotensin system inhibiting medicine (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory medicine (NSAID, including COX-2 inhibitor) alone or with a thiazide diuretic may increase the risk of renal impairment, including possible acute renal failure. These effects are usually reversible. This includes use in fixed-combination products containing more than one class of medicine. The combination of these agents should be administered with caution, especially in the elderly, volume-depleted, and in patients with pre-existing renal impairment. Renal function (serum creatinine) should be monitored after initiation of concomitant therapy, and periodically thereafter. The antihypertensive effect of angiotensin II receptor antagonists, including irbesartan, may be attenuated by NSAIDs including selective COX-2 inhibitors.

The use of irbesartan/hydrochlorothiazide in combination with an ACE inhibitor is contraindicated in patients with diabetic nephropathy (see **CONTRAINDICATIONS** and **INTERACTIONS WITH OTHER MEDICINES**).

Renin inhibitor

The combination of irbesartan/hydrochlorothiazide with aliskiren-containing medicinal products is contraindicated in patients with diabetes mellitus or moderate to severe renal impairment and is not recommended in other patients (see **CONTRAINDICATIONS**).

Angiotensin-Converting Enzyme inhibitors (ACE inhibitors)

The use of irbesartan/hydrochlorothiazide in combination with an ACE inhibitor is contraindicated in patients with diabetic nephropathy and is not recommended in other patients.

Medicines used during surgery - The effects of nondepolarizing muscle relaxants (e.g., tubocurarine), preanaesthetics and anaesthetics used in surgery may be potentiated by hydrochlorothiazide; dosage adjustments may be required. Preanesthetic and anaesthetic agents should be given in reduced dosage, and if possible, hydrochlorothiazide therapy discontinued one week prior to surgery.

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.

Pressor amines (eg noradrenaline) - Due to the thiazide component there is a possible decreased response to pressor amines but not sufficient to preclude their use.

Corticosteroids, ACTH - Intensified electrolyte depletion, particularly hypokalemia can occur with thiazide use.

Digitalis glycosides

Thiazide induced hypokalaemia or hypomagnesaemia favour the onset of digitalis-induced cardiac arrhythmias.

Other interactions - The hypoglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides. Anticholinergic agents (eg atropine) 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 medicines (eg cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

ADVERSE EFFECTS

The combination of irbesartan and hydrochlorothiazide has been evaluated for safety in approximately 2750 subjects in clinical studies, including 1540 hypertensive patients treated for over 6 months and over 960 patients treated for one year or more. Adverse events in patients receiving irbesartan/hydrochlorothiazide were generally mild and transient with no relationship to dose. The incidence of adverse events was not related to age, gender, or race.

In placebo-controlled clinical studies, including 898 irbesartan/hydrochlorothiazide-treated patients (usual duration of treatment 2 to 3 months), discontinuations due to any clinical or laboratory adverse event were 3.6 percent for irbesartan/hydrochlorothiazide-treated patients and 6.8 percent for placebo-treated patients (p=0.023).

Adverse events occurring in at least 1% of patients treated with irbesartan/hydrochlorothiazide, in placebo controlled trials are shown in the table below.

The incidences of the same adverse events in the placebo, irbesartan and hydrochlorothiazide control groups are also shown.

Adverse Events in Placebo-Controlled Hypertension Trials

BODY SYSTEM/EVENT	Incidence Percentage (%) of Patients			
	Irbesartan/HCTZ n=898	Irbesartan n=400	HCTZ n=380	Placebo n=236
<i>General</i>				
Chest pain	1.8	1.5	1.6	1.3
Fatigue	6.5 *	4.0	3.2	3.0
Influenza	2.8	2.0	1.8	1.3
<i>Cardiovascular</i>				
Oedema	3.1	1.5	1.6	2.5
Tachycardia	1.2	0.5	0.5	0.4
<i>Dermatology</i>				
Rash	1.2	1.8	3.2	1.7
<i>Gastrointestinal</i>				
Abdominal pain	1.7	1.5	1.6	0.8
Anorectal disorder	1.0	0.3	0	0.4
Diarrhoea	2.1	2.8	1.1	3.4
Dyspepsia/heartburn	2.1	0.3	1.6	0.8
Nausea/vomiting	3.2 *	1.5	2.4	0.4
<i>Immunology/Sensitivity disorder</i>				
Allergy	1.1	0.5	0.5	0
<i>Musculoskeletal/Connective Tissue</i>				
Musc/skeletal pain	6.5	6.0	9.7 *	4.7
Muscle cramp	1.0	0.8	2.1	1.3
Musculoskeletal trauma	1.3	2.0	1.8	0.8
<i>Nervous System</i>				
Anxiety/nervousness	1.0	1.0	0.5	1.7
Dizziness	7.6	5.5	4.7	4.2
Dizziness orthostatic	1.1	1.0	0.8	0.4
Headache	11.0 *	9.3 *	11.6	16.1
<i>Renal/Genitourinary</i>				
Abnormal urination	1.9	0.5	2.1	0.8
UTI	1.6	1.5	2.4	2.5
<i>Respiratory</i>				
Cough	2.2	2.3	2.6	3.0
Pharyngitis	2.1	2.3	2.9	1.7
Rhinitis	1.9	2.0	1.6	2.5
Sinus abnormality	2.9	4.5	3.2	4.7
Upper respiratory infection	5.6	8.3	7.1	5.5

* Statistically significant difference compared with placebo, p<0.05

Adverse effects (clinical events probably or possibly related to therapy as determined by the clinical investigator) that occurred in more than 2 hypertensive patients when they were taking irbesartan/hydrochlorothiazide and no additional study medications in premarketing clinical trials involving 2700 subjects, and that were not reported in the above tabulation of adverse events, are listed in the following section.

These adverse effects have been classified using standard terminology and are categorized by body system. They are listed in order of decreasing frequency according to the following definitions:

Common: those adverse effects occurring on one or more occasions in at least 1/100 but less than 1/10 patients; *uncommon*: adverse reactions occurring in at least 1/1000 but less than 1/100 patients; *rare*: those adverse reactions occurring in less than 1/1000 patients.

Cardiovascular:

Uncommon – bradycardia, disturbance of cardiac rhythm, subjective disturbance of cardiac rhythm, disturbance of ventricular rhythm, ECG abnormality, flushing, hypotension, orthostatic hypotension, syncope.

Dermatologic:

Uncommon – pruritus, skin discomfort.

Endocrine/Metabolic:

Common - sexual dysfunction.

Uncommon – diabetes, gout, hot flashes, libido changes.

Gastrointestinal:

Uncommon – constipation, decreased appetite, abdominal distention, dry mouth, epigastric pain, flatulence, gastroesophageal reflux.

General:

Uncommon - cold sensation, hyperhidrosis, malaise, weakness, weight gain.

Musculoskeletal/Connective Tissue:

Uncommon - abnormal reflexes, muscle ache, myalgia, extremity swelling, extremity weakness.

Nervous System:

Uncommon - coordination disturbance, depression, emotional lability/disturbance, numbness, paresthesia, sleep disturbance, somnolence, vertigo.

Respiratory:

Uncommon - dry nasopharynx, dyspnea, wheezing.

Special Senses:

Uncommon - abnormal hearing, taste disturbance, vision disturbance.

Other clinical adverse reactions reported with the use of irbesartan or hydrochlorothiazide alone include:

Cardiovascular: subjective rhythm disturbance, flushing, ECG abnormality, cardiac murmur, cardiac rhythm disturbance, orthostatic hypotension, atrial rhythm disturbance, conduction disorder, myocardial infarction.

Dermatologic: facial erythema, dermatitis, acne, scalp-hair abnormality.

Endocrine/Metabolic/ Electrolyte Imbalance: breast disorder, hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia and hypokalaemia).

Gastrointestinal: abnormal stool, increased appetite, oral lesion, dysphagia, oesophagitis, anorexia, gastric irritation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis, xanthopsia.

General: weakness, weight gain, warmth sensation, pain.

Haematopoietic: leucopenia, neutropenia/agranulocytosis, thrombocytopenia, anaemia, aplastic anaemia, haemolytic anaemia.

Immunology/ Sensitivity Disorder: upper extremity oedema, head/neck oedema, photosensitivity reactions, fever, urticaria, necrotizing angitis, (vasculitis, cutaneous vasculitis), respiratory distress (including pneumonitis and pulmonary oedema), anaphylactic reactions, toxic epidermal necrolysis.

Musculoskeletal/Connective Tissue: arthritis, stiffness lower extremity, muscle spasm, weakness.

Nervous System: stress related disorder, tremor, disturbing dreams, restlessness.

Renal/Genitourinary: urination abnormality, renal dysfunction, interstitial nephritis.

Respiratory: epistaxis.

Special Senses: eye disturbance - other, eyelid abnormality, visual field abnormality, medication bad taste, transient blurred vision.

Postmarketing Experience: As with other angiotensin-II receptor antagonists, rare cases of hypersensitivity reactions (urticaria, angioedema) have been reported. The following have also been reported during post-marketing surveillance: vertigo, asthenia, hyperkalemia, thrombocytopenia, myalgia, jaundice, elevated liver function tests, hepatitis, arthralgia, tinnitus and impaired renal function including cases of renal failure in patients at risk.

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

DOSAGE AND ADMINISTRATION

Irbesartan/hydrochlorothiazide should not be initiated as first-line therapy. The daily dose can be administered with or without food.

Replacement Therapy

The combination may be substituted for the titrated components at the same dose level.

Dose Titration by Clinical Effect

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

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

Doses higher than irbesartan/hydrochlorothiazide 300mg/25mg once daily are not recommended. When necessary, irbesartan/hydrochlorothiazide may be administered with another antihypertensive medicine.

Patients with Intravascular Volume Depletion

In severely volume-depleted and/or sodium-depleted patients, such as those treated vigorously with diuretics, the condition should be corrected prior to administration of irbesartan/hydrochlorothiazide.

Elderly Patients

No dosage reduction is generally necessary for daily dosage of irbesartan/hydrochlorothiazide 150mg/12.5mg in the elderly.

Patients with Renal Impairment

No dosage reduction is generally necessary for daily dosage of irbesartan/hydrochlorothiazide 150mg/12.5mg in patients with mild-to-moderate renal impairment (creatinine clearance >30mL/min).

Patients with Hepatic Impairment

No dosage reduction is thought to be necessary in patients with mild to moderate hepatic impairment as the pharmacokinetics of neither irbesartan nor hydrochlorothiazide are affected by hepatic impairment. Due to the hydrochlorothiazide component, irbesartan/hydrochlorothiazide should be used with caution in patients with severe hepatic impairment (see **PRECAUTIONS – Impaired Hepatic Function**).

OVERDOSAGE

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

Experience in adults exposed to irbesartan doses of up to 900mg/day for 8 weeks revealed no toxicity. No specific information is available on the treatment of overdose with irbesartan/hydrochlorothiazide. The patient should be closely monitored, and the treatment should be symptomatic and supportive, including fluid and electrolyte replacement. Irbesartan is not removed from the body by haemodialysis.

The most common signs and symptoms observed in adults exposed to hydrochlorothiazide are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If a cardiac glycoside (e.g., digoxin) or other antiarrhythmic medicines (e.g., sotalol) has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

PRESENTATION AND STORAGE CONDITIONS

Irbesartan/HCT Sandoz 150mg/12.5mg - apricot, oval biconvex film-coated tablet, debossed with 150H on one side.

Irbesartan/HCT Sandoz 300mg/12.5mg - apricot, oval biconvex film-coated tablet, debossed with 300H on one side.

Irbesartan/HCT Sandoz 300mg/25mg – dark pink, oval biconvex film-coated tablet, debossed with 300 on one side and 25H on the other side.

Available in *bottles and blister packs of 30 tablets.

** Not currently marketed in Australia*

Store below 25 °C.

Protect from moisture.

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road
Macquarie Park, NSW 2113
Australia
Tel: 1800 634 500

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG): 28/10/2011

Date of most recent amendment: 15/06/2017