PRODUCT INFORMATION

ABISART HCTZ 150/12.5, 300/12.5 & 300/25

Irbesartan Hydrochlorothiazide

1. NAME OF THE MEDICINE

Irbesartan and hydrochlorothiazide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ABISART HCTZ is an oral antihypertensive agent combining a nonpeptide angiotensin II receptor (AT 1 subtype) antagonist, irbesartan, and a thiazide diuretic, hydrochlorothiazide. The active ingredients in ABISART HCTZ 150/12.5, 300/12.5 & 300/25 (herein referred to as ABISART HCTZ) tablets are irbesartan and 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.

ABISART HCTZ 150/12.5 contains the active ingredients 150 mg of irbesartan and 12.5 mg of hydrochlorothiazide, ABISART HCTZ 300/12.5 contains 300 mg of irbesartan and 12.5 mg of hydrochlorothiazide, and ABISART HCTZ 300/25 contains 300 mg of irbesartan and 25 mg of hydrochlorothiazide.

Excipient with known effect:
Each tablet of ABISART HCTZ 150/12.5 mg, 300/25 mg and 300/12.5 mg contains 42.50 mg, 85.00 mg and 97.50 mg of lactose monohydrate respectively. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

ABISART HCTZ 150/12.5 tablets contain the active ingredients irbesartan 150 mg and hydrochlorothiazide 12.5 mg and are pink to red, film-coated, oval-shaped and debossed with ‘IH1” on one side and plain on the other.

ABISART HCTZ 300/12.5 tablets contain the active ingredients irbesartan 300 mg and hydrochlorothiazide 12.5 mg and are yellow, film-coated, oval-shaped and debossed with ‘IH3” on one side and plain on the other.

ABISART HCTZ 300/25 tablets contain the active ingredients irbesartan 300 mg and hydrochlorothiazide 25 mg and are pink to red, film-coated, oval-shaped and debossed with ‘IH2” on one side and plain on the other.

ABISART HCTZ tablets are formulated for oral administration.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ABISART HCTZ tablets are indicated for the treatment of hypertension.

Treatment should not be initiated with this fixed-dose combination.

4.2 DOSE AND METHOD OF ADMINISTRATION

ABISART HCTZ tablets 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:

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

Doses higher than 300 mg irbesartan/25 mg hydrochlorothiazide once daily are not recommended. When necessary, ABISART HCTZ 150/12.5, 300/12.5 & 300/25 tablets may be administered with another antihypertensive drug.

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 fixed dose combination tablets of irbesartan and hydrochlorothiazide.

Elderly Patients

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

Patients with Renal Impairment

No dosage reduction is generally necessary for daily dosage of irbesartan 150 mg/ hydrochlorothiazide 12.5 mg 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 and hydrochlorothiazide tablets should be used with caution in patients with severe hepatic impairment (see Section 4.4 SPECIAL WARNING AND PRECAUTIONS FOR USE – Use in hepatic impairment).

4.3 CONTRAINDICATIONS

ABISART HCTZ 150/12.5, 300/12.5 & 300/25 tablets are contraindicated in patients who are hypersensitive to irbesartan, sulfonamide-derived drugs (e.g. thiazides), or to any other component of ABISART HCTZ tablets. In general, hypersensitivity reactions are more likely to occur in patients with a history of allergy or bronchial asthma.

ABISART HCTZ 150/12.5, 300/12.5 & 300/25 tablets are contraindicated in patients who are anuric.

Do not coadminister ABISART HCTZ 150/12.5, 300/12.5 & 300/25 with aliskiren-containing medicines in patients with diabetes or with moderate to severe renal impairment.

Pregnancy (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in pregnancy).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

This medicine contains lactose as an excipient. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Hypotension - Volume - Depleted Patients

Fixed dose combination tablets of irbesartan and hydrochlorothiazide have 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 fixed dose combination tablets of Irbesartan and hydrochlorothiazide. Thiazides may potentiate the action of other antihypertensive drugs (see INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Dual blockade of the Renin-Angiotensin-Aldosterone System (RAAS) with aliskiren containing medicinal products

Dual blockade of the RAAS by combining fixed dose combination tablets of irbesartan and hydrochlorothiazide with aliskiren is not recommended since there is an increased risk of hypotension, hyperkalemia, and changes in renal function. The use of fixed dose combination tablets of irbesartan and hydrochlorothiazide in combination with aliskiren is contraindicated in patient with diabetes mellitus or renal impairment (see Section 4.3 CONTRAINDICATIONS).

Renal Artery Stenosis

See comments under Section 4.4 SPECIAL WARNING AND PRECAUTIONS FOR USE - Renal Impairment, below.

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 fixed dose combination tablets of irbesartan and hydrochlorothiazide is not recommended.

Postsympathectomy

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

Fluid and Electrolyte Imbalance

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

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

Metabolic and Endocrine Effects

Hyperuricaemia 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 12.5 mg hydrochlorothiazide dose contained in fixed dose combination tablets of irbesartan and 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.

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.

Use in hepatic impairment

Fixed dose combination tablets of irbesartan and 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.

Use in renal impairment

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function during therapy with fixed dose combination tablets of irbesartan and 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 drugs that affect this system has been associated with oliguria and/or progressive azotaemia 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 fixed dose combination tablets of irbesartan and hydrochlorothiazide cannot be excluded.

There is no experience with fixed dose combination tablets of irbesartan and hydrochlorothiazide in patients with a recent renal transplant.

Fixed dose combination tablets of irbesartan and hydrochlorothiazide are not recommended for patients with severe renal disease (creatinine clearance $\leqslant$ 30 mL/min) (see Section 4.3 CONTRAINDICATIONS). Hydrochlorothiazide-associated precipitation of azotaemia may occur in patients with impaired renal function. As experience is limited in patients with a creatinine clearance >30 and <60mL/min, fixed dose combination tablets of irbesartan and hydrochlorothiazide should be administered with caution to such patients.

Use in the elderly

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

Paediatric Use

Safety and effectiveness in paediatric patients have not been established.

Effects on Laboratory Tests

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

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 fixed dose combination tablets of irbesartan and hydrochlorothiazide alone. No patient discontinued taking fixed dose combination tablets of irbesartan and hydrochlorothiazide due to increased BUN. One patient discontinued taking fixed dose combination tablets of irbesartan and hydrochlorothiazide due to a minor increase in creatinine.

Haemoglobin: Mean decreases of approximately 0.2 g/dL occurred in patients treated with fixed dose combination tablets of irbesartan and hydrochlorothiazide alone, but were rarely of clinical importance. This compared to a mean of 0.4 g/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 and hydrochlorothiazide tablets, 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 hypokalaemia (serum potassium <3.5 mmol/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 Section 4.4 SPECIAL WARNING AND PRECAUTIONS FOR USE –- Fluid and Electrolyte Imbalance).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

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

Based on experience with the use of other drugs that affect the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, or salt substitutes containing potassium with irbesartan may lead to increases in 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 drugs (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.

Cardiac glycosides (e.g. digoxin) and other antiarrhythmic drugs (e.g. sotalol)

Diuretic-induced hypokalaemia may accentuate cardiac arrhythmias.

Calcium salts

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

Colestyramine resin and colestipol HCl

May delay or decrease absorption of hydrochlorothiazide. Irbesartan and hydrochlorothiazide tablets 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. Reversible increases in lithium concentrations have also been very rarely reported with irbesartan. Therefore, if coadministration of fixed dose combination tablets of irbesartan and hydrochlorothiazide and lithium proves necessary, careful monitoring of serum lithium levels is necessary.

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 and hydrochlorothiazide tablets may potentiate the actions of other antihypertensive drugs, especially ganglionic or peripheral adrenergic-blocking drugs. 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 drugs and thiazide diuretics

Concomitant use of a renin-angiotensin system inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), and an anti-inflammatory drug (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 drug. 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.

Renin inhibitor

The combination of fixed dose combination tablets of irbesartan and 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 Section 4.4 SPECIAL WARNING AND PRECAUTIONS FOR USE – Use in renal impairment).

Drugs used during surgery

The effects of non-depolarising 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 (e.g. 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 hypokalaemia can occur with thiazide use.

Other interactions

The hypoglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides. Anticholinergic agents (e.g. 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 drugs (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

4.6 FERTILITY, PREGNANCY AND LACTATION

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 650 mg/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 300 mg/day).

Use in pregnancy (Category D)

Drugs 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, fixed dose combination tablets of irbesartan and hydrochlorothiazide should be discontinued as soon as possible.

The use of drugs 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 drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and foetuses 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 fixed dose combination tablets of irbesartan and hydrochlorothiazide as soon as possible.

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, thrombocytopaenia and possibly other adverse reactions which have occurred in the adult.

No teratogenic effects were seen in rats given irbesartan and hydrochlorothiazide in combination at doses as high as 150/150 mg/kg/day. When pregnant rats were treated with irbesartan alone from day 0 to day 20 of gestation, at doses of 50 mg/kg/day and higher, transient effects (increased renal pelvic cavitation, hydroureter or subcutaneous oedema) were noted in full term rat foetuses but not in young animals necropsied after six weeks of age. In pregnant rabbits, at doses of 30 mg/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 fixed combination tablets of irbesartan and 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 drug, taking into account the importance of irbesartan and hydrochlorothiazide tablets to the therapy of the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of fixed dose combination tablets of irbesartan and hydrochlorothiazide on the ability to drive motor vehicles or operate machinery have not been specifically studied, but based on its pharmacodynamic properties fixed dose combination tablets of irbesartan and hydrochlorothiazide are 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE 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 fixed dose combination tablets of irbesartan and 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.

Table: 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**
General				
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
Cardiovascular				
Oedema	3.1	1.5	1.6	2.5
Tachycardia	1.2	0.5	0.5	0.4
Dermatology				
Rash	1.2	1.8	3.2	1.7
Gastrointestinal				
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
Immunology/Sensitivity disorder				
Allergy	1.1	0.5	0.5	0
Musculoskeletal/Connective Tissue				
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

Table: 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**
Nervous System				
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
Renal/Genitourinary				
Abnormal urination	1.9	0.5	2.1	0.8
UTI	1.6	1.5	2.4	2.5
Respiratory				
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 reactions (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 reactions have been classified using standard terminology and are categorised by body system. They are listed in order of decreasing frequency according to the following definitions:

common: those adverse reactions 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; dyspnoea; 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: leucopaenia, neutropaenia/agranulocytosis, thrombocytopaenia, anaemia, aplastic anaemia, haemolytic anaemia.

Immunology/Sensitivity Disorder: upper extremity oedema, head/neck oedema, photosensitivity reactions, fever, urticaria, necrotizing angiitis, (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, 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.

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

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Experience in adults exposed to irbesartan doses of up to 900 mg/day for 8 weeks revealed no toxicity. No specific information is available on the treatment of overdosage with irbesartan and hydrochlorothiazide tablets. 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 (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If a cardiac glycoside (e.g . digoxin) or other antiarrhythmic drugs (e.g. sotalol) has also been administered, hypokalaemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

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 localised 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.

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 12.5 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 300/12.5 mg combination may respond when uptitrated to 300/25 mg. In these patients, an incremental blood pressure lowering effect was observed for both SBP and DBP (13.3 and 8.3 mm Hg, respectively).

Once daily dosing with 150 mg irbesartan and 12.5 mg 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, fixed dose combination tablets of irbesartan and hydrochlorothiazide 150/12.5 once daily produced consistent reduction in blood pressure over the 24 hours period with a mean 24-hour placebo-subtracted systolic/diastolic reductions of 15.8/10.0 mmHg. 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 25 mg hydrochlorothiazide alone after 4 weeks' treatment, the addition of irbesartan (with dose-to-response uptitration from 75 mg to 150 mg at 6 weeks) produced mean systolic/diastolic reductions at 12 weeks which were 11.1/7.2 mm Hg 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.

5.2 PHARMACOKINETIC PROPERTIES

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

Absorption

The oral bioavailabilities of irbesartan and hydrochlorothiazide measured after administration of fixed dose combination of irbesartan and hydrochlorothiazide tablets 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 and hydrochlorothiazide tablets. 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 L/kg). Hydrochlorothiazide is 68% protein-bound in the plasma, and its apparent volume of distribution is 0.83 -1.141 L/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 metabolised 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 metabolised by, nor does it substantially induce or inhibit most isoenzymes commonly associated with drug metabolism (i.e. CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2D6, or CYP2E1). Irbesartan does not induce nor inhibit isoenzyme CYP3A4.

Hydrochlorothiazide is not metabolised.

Excretion

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 (t½) of irbesartan from plasma is 11-15 hours. The total body clearance of intravenously administered irbesartan is 157-176 mL/min, of which 3.0-3.5 mL/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 (t½) 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 (Cmax) 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 t½ of irbesartan are approximately 20-25% greater in blacks than in whites; the peak plasma concentrations (Cmax) 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 <20 mL/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 are not significantly altered.

5.3 PRECLINICAL SAFETY DATA

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 non-disjunction assay in *Aspergillus nidulans*).

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 500 mg/kg/day (male rats) and 1000 mg/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 300 mg/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 600 mg/kg/day, or in male and female rats at doses up to approximately 100 mg/kg/day. The studies, however, uncovered equivocal evidence for hepatocarcinogenicity in male mice treated with hydrochlorothiazide at approximately 600 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- lactose monohydrate
- microcrystalline cellulose
- croscarmellose sodium
- colloidal anhydrous silica
- hypromellose
- magnesium stearate

In addition, the 150/12.5 and 300/25 tablets contain:

- Opadry 03G54386 Pink (Proprietary Ingredient No.107731)

And, the 300/12.5 tablets contain:

- Iron oxide yellow
- Opadry 03G52390 Yellow (Proprietary Ingredient No. 107730)

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

The tablets are available in blister (PA/Al/PVC/Al or PVC/PCTFE(Aclar)/Al) packs of 30 and 90*.

Some strengths, pack sizes and/or pack types may not be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

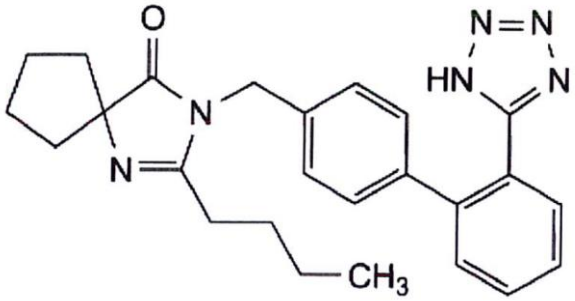
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

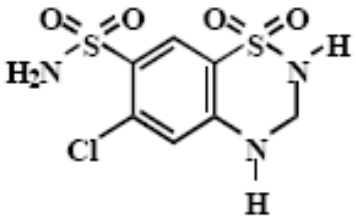
Chemical names: Irbesartan: 2-butyl-3-[(2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,3-diazaspiro [4,4] non-1-en-4-one

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

Chemical structure



Irbesartan:



Hydrochlorothiazide:

Molecular formula:

Irbesartan: $C_{25}H_{28}N_6O$

Hydrochlorothiazide: $C_7H_8ClN_3O_4S_2$

Molecular weights:

Irbesartan: 428.5

Hydrochlorothiazide: 297.7

CAS numbers:

Irbesartan: CAS-138402-11-6

Hydrochlorothiazide: CAS-58-93-5

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8. SPONSOR

Sun Pharma ANZ Pty Ltd.

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Australia

customerservice.aus@sunpharma.com

Tel: 1800 726 229

9. DATE OF FIRST APPROVAL

06/11/2018

10. DATE OF REVISION

09/08/2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of New Information
4.5	Updated medicine name to comply with International Harmonisation of Ingredient Names

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