SUMMARY OF PRODUCT CHARACTERISTICS

IRB-H

Irbesartan and Hydrochlorothiazide Tablets

R_x Only

1. NAME OF THE MEDICINAL PRODUCT:

Irbesartan and Hydrochlorothiazide Tablets	150/12.5 mg
(TRADE) NAME OF PRODUCT	**:** IRB-H 150/12.5
STRENGTH	: 150/12.5 mg
PHARMACEUTICAL FORM	**:** Film-coated Tablet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Irbesartan and Hydrochlorothiazide Tablets 150/12.5 mg

Each film-coated tablet contains Irbesartan Ph.Eur. 150 mg and Hydrochlorothiazide Ph.Eur. 12.5 mg

3. DESCRIPTION

Irbesartan and Hydrochlorothiazide Tablets 150/12.5 mg

Peach coloured, film-coated biconvex oval shaped tablets, debossed with “H 35” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension.

This fixed dose combination is indicated in adult patients whose blood pressure is not adequately controlled on Irbesartan or hydrochlorothiazide alone.

4.2 Posology and method of administration

Irbesartan and Hydrochlorothiazide Tablets can be taken once daily, with or without food.

Dose titration with the individual components (i.e. irbesartan and hydrochlorothiazide) may be recommended.

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

- *Irbesartan and Hydrochlorothiazide Tablets* 150 mg/12.5 mg may be administered in patients whose blood pressure is not adequately controlled with hydrochlorothiazide or Irbesartan 150 mg alone;

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

When necessary, Irbesartan and Hydrochlorothiazide Tablets may be administered with another antihypertensive medicinal product. (Refer Interaction with other medicinal products and other forms of interaction section).

Renal impairment

due to the hydrochlorothiazide component, Irbesartan and Hydrochlorothiazide is not recommended for patients with severe renal dysfunction (creatinine clearance < 30 ml/min). Loop diuretics are preferred to thiazides in this population. No dosage adjustment is necessary in patients with renal impairment whose renal creatinine clearance is > 30 ml/min (Refer Contraindications and Special warnings and precautions for use section).

Hepatic impairment

Irbesartan and Hydrochlorothiazide is not indicated in patients with severe hepatic impairment. Thiazides should be used with caution in patients with impaired hepatic function. No dosage adjustment of Irbesartan and Hydrochlorothiazide is necessary in patients with mild to moderate hepatic impairment (Refer Contraindications section).

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

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

Route of Administration

Oral

4.3 Contraindications

Concomitant use of (active ingredient of ARB) with aliskiren-containing products is contra indicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2).

- Hypersensitivity to the active substances or to any of the excipient listed in section 6.1, or to other sulfonamide-derived substances (hydrochlorothiazide is a sulfonamide-derived substance)
- Second and third trimesters of pregnancy (Refer Special warnings and precautions for use and Pregnancy and lactation section)
- Severe renal impairment (creatinine clearance < 30 ml/min)
- Refractory hypokalaemia, hypercalcaemia
- Severe hepatic impairment, biliary cirrhosis and cholestasis

4.4 Special warnings and precautions for use

Hypotension - Volume-depleted patients: Irbesartan and Hydrochlorothiazide has been rarely associated with symptomatic hypotension in hypertensive patients without other risk factors for hypotension. Symptomatic hypotension may be expected to occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before initiating therapy with Irbesartan and Hydrochlorothiazide.

Renal artery stenosis - Renovascular hypertension: there is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with angiotensin converting enzyme inhibitors or angiotensin-II receptor antagonists. While this is not documented with IRB-H a similar effect should be anticipated.

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

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

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy: as with other vasodilators, special caution isindicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Primary aldosteronism: patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of Irbesartan and Hydrochlorothiazide is not recommended.

Metabolic and endocrine effects: thiazide therapy may impair glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Latent diabetes mellitus may become manifest during thiazide therapy.

Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy; however at the 12.5mg dose contained Irbesartan and Hydrochlorothiazide, minimal or no effects .Hyperuricaemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Electrolyte imbalance: as for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloremic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting.

Although hypokalaemia may develop with the use of thiazide diuretics,concurrent therapy with irbesartan may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH. Conversely, due to the irbesartan component of Irbesartan and 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. Potassium-sparing diuretics,potassium supplements or potassium-containing salts substitutes should be co-administered cautiously with Irbesartan and Hydrochlorothiazide (Refer Interaction with other medicinal products and other forms of interaction section).

There is no evidence that irbesartan would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.

Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnaesemia.

Lithium: the combination of lithium and Irbesartan and Hydrochlorothiazide is not recommended (Refer Interaction with other medicinal products and other forms of interaction section).

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

General:

in patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including grenal artery stenosis), treatment with angiotensin converting enzyme inhibitors or angiotensin-II receptor antagonists that affect this system has been associated with acute hypotension, azotaemia, oliguria, or rarely acute renal failure (see section 4.5). As with any antihypertensive agent, excessive blood pressure decrease in patients with ischemic cardiopathy or ischemic cardiovascular disease could result in a myocardial infarction or stroke.

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

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

Photosensitivity reactions may cause with thiazides diuretics (Refer Undesirable effects). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Pregnancy: Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (Refer Contraindications and Pregnancy and lactation section).

Lactose: this medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Non-melanoma skin cancer

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

ACE inhibitors: The use of (active ingredient of ARB) with an ACE inhibitor may increase the risk of hyperkalaemia, hypotension, and syncope, particularly in patients with atherosclerotic disease or heart failure, or in diabetics who have end–organ damage. Such combinations should be reserved for selected cases with close monitoring of renal function.

Other antihypertensive agents:

Other antihypertensive agents: the antihypertensive effect of Irbesartan and Hydrochlorothiazide may be increased with the concomitant use of other antihypertensive agents. Irbesartan and hydrochlorothiazide (at doses up to 300 mg irbesartan/25 mg hydrochlorothiazide) have been safely administered with other antihypertensive agents including calcium channel blockers and beta-adrenergic blockers. Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with irbesartan with or without thiazide diuretics unless the volume depletion is corrected first (Refer Special warnings and precautions for use section).

Lithium: reversible increases in serum lithium concentrations and toxicity may occur during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Similar effects have been very rarely occur with irbesartan so far. Furthermore, renal clearance of lithium is reduced by thiazides so the risk of lithium toxicity could be increased with Irbesartan and Hydrochlorothiazide. Therefore, the combination of lithium and Irbesartan and Hydrochlorothiazide is not recommended (Refer Special warnings and precautions for use section). If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

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

Medicinal products affected by serum potassium disturbances: periodic monitoring of serum potassium is recommended when IRB-H is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, anti arrhythmics).

Non-steroidal anti-inflammatory drugs: when angiotensin II antagonists are administered simultaneously with non-steroidal anti- inflammatory drugs (i.e. selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.

As with ACE inhibitors, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Additional information on irbesartan interactions: in clinical studies, the pharmacokinetic of irbesartan is not affected by hydrochlorothiazide. Irbesartan is mainly metabolised by CYP2C9 and to a lesser extent by glucuronidation. No significant pharmacokinetic or pharmacodynamic interactions were observed when irbesartan was co administered withwarfarin, a medicinal product metabolised by CYP2C9. The effects of CYP2C9 inducers such as rifampicin on the pharmacokinetic of irbesartan have not been evaluated. The pharmacokinetic of digoxin was not altered by co-administration of irbesartan.

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

*Alcohol:*potentiation of orthostatic hypotension may occur;

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

Colestyramine and Colestipol resins: absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. IRB-H should be taken at least one hour before or four hours after these medications;

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

Digitalis glycosides: hiazide induced hypokalaemia or hypo magnaesemia favour the onset of digitalis-induced cardiac arrhythmias (see section 4.4);

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

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

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

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

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

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

4.6 Pregnancy and lactation

Pregnancy: the use of AIIRAs is not recommended during the first trimester of pregnancy (Refer Special warnings and precautions for use section). The use of AIIRAs is contraindicated during the second and third trimester of pregnancy (Refer Contraindications and Special warnings and precautions for use section).

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

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

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

Infants whose mothers have taken AIIRAs should be closely observed for hypotension (Refer Contraindications and Special warnings and precautions for use section).

Thiazides cross the placental barrier and appear in cord blood. They may cause a decrease in placental perfusion, foetal electrolyte disturbances and possibly other reactions that have occurred in the adults. Neonatal thrombocytopenia, or foetal or neonatal jaundice may occur with maternal thiazide therapy.

Black A/s : 210 x 420 mm

AUROBINDO Packaging Development	**Product Name**	**Component**	**Item Code**	**Date & Time**
	IRB-H	Leaflet	P1515882	26.12.2024 & 05.10 pm
	Customer / Country	**Version No.**	**Reason of Issue**	**No. of Colours : 1**
	Malaysia_U3	13	Submission	
Team Leader: Kiran	**Dimensions**			
Initiator: Shirisha	210 x 420 mm			
Design Agency Advnt (Rakesh)	**Pharma Code**			
	15882			

Additional Information: Word Repalcement 29.11.2022

Since Irbesartan and Hydrochlorothiazide contains hydrochlorothiazide, it is not recommended during the first trimester of pregnancy. A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy.

Lactation:

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Based on its pharmacodynamic properties, Irbesartan and Hydrochlorothiazide is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur during treatment of hypertension.

4.8 Undesirable effects

Irbesartan/hydrochlorothiazide combination

The frequency of adverse reactions listed below:

Table1: Adverse Reactions with use of Irbesartan/hydrochlorothiazid combination

Cardiac disorders	Uncommon	syncope, hypotension, tachycardia, oedema
Nervous system disorders	Common	dizziness
	Uncommon	orthostatic dizziness
	Not known	headache
Ear and labyrinth disorders	Not known	tinnitus
Respiratory, thoracic and mediastinal disorders	Not known	cough
	Very rare	Acute respiratory distress syndrome (ARDS)
Gastrointestinal disorders	Common	nausea/vomiting
	Uncommon	diarrhoea
	Not known	dyspepsia, dysgeusia
Renal and urinary disorders	Common	abnormal urination
	Not known	impaired renal function including isolated cases of renal failure in patients at risk (Refer Special warnings and precautions for use section)
Musculoskeletal and connective tissue disorders	Uncommon	swelling extremity
	Not known	arthralgia, myalgia
Metabolism and nutrition disorders	Not known	hyperkalaemia
Vascular disorders	Uncommon	flushing
General disorders and administration site conditions	Common	fatigue
Immune system disorders	Not known	cases of hypersensitivity reactions such as angioedema,rash, urticaria
Hepatobiliary disorders	Uncommon Not known	hepatitis, abnormal liver function
Reproductive system and breast disorders	Uncommon	sexual dysfunction, libido changes
Eye disorders	Not known	Choroidal effusion, acute myopia, acute angleclosure glaucoma

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

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

General disorders and administrationsite conditions	Uncommon	chest pain

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

Cardiac disorders	Not known	cardiac arrhythmias
Blood and lymphatic system disorders	Not known	aplastic anaemia, bone marrow depression,neutropenia/agranulocytosis, haemolytic anaemia, leucopenia, thrombocytopenia
Nervous system disorders	Not known	vertigo, paraesthesia, light-headedness, restlessness
Eye disorders	Not known	transient blurred vision, xanthopsia, acute myopia and secondary acute angle-closure glaucoma, choroidal effusion
Respiratory, thoracic and mediastinal disorders	Not known	respiratory distress (including pneumonitis and pulmonary oedema)
	very rare	Acute respiratory distress syndrome (ARDS)
Gastrointestinal disorders	Not known	pancreatitis, anorexia, diarrhoea, constipation, gastric irritation, sialadenitis, loss of appetite
Renal and urinary disorders	Not known	interstitial nephritis, renal dysfunction
Skin and subcutaneous tissue disorders	Not known	anaphylactic reactions, toxic epidermal necrolysis, necrotizing angitis (vasculitis, cutaneous vasculitis),cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, photosensitivity reactions, rash, urticaria
Musculoskeletal and connective tissue disorders	Not known	weakness, muscle spasm
Vascular disorders	Not known	postural hypotension
General disorders and administration site conditions	Not known	Fever
Hepatobiliary disorders	Not known	jaundice (intrahepati cholestatic jaundice)
Psychiatric disorders	Not known	depression, sleep disturbances

The dose dependent adverse events of hydrochlorothiazide (particularly electrolyte disturbances) may increase when titrating the hydrochlorothiazide. Neoplasms benign, malignant and unspecified (incl cysts and polyps) Frequency 'not known': Non-melanoma skin cancer (Basal cell carcinoma and squamous cell carcinoma)

Description of selected adverse reactions

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed

4.9 Overdose

No specific information is available on the treatment of overdose with Irbesartan and Hydrochlorothiazide.

The patient should be closely monitored, and the treatment should be symptomatic and supportive.

Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and/or gastric lavage. Activated charcoal may be useful in the treatment of overdose.

Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacements given quickly.

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

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Irbesartan and Hydrochlorothiazide is a combination of an angiotensin-II receptor antagonist, irbesartan, and a thiazide diuretic, hydrochlorothiazide.

The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Irbesartan is a potent, orally active, selective angiotensin-II receptor (AT1 subtype) antagonist. It is expected to block all actions of angiotensin-II mediated by the AT1 receptor, regardless of the source or route of synthesis of angiotensin-II. The selective antagonism of the angiotensin-II (AT1) receptors results in increases in plasma renin levels and angiotensin-II levels, and a decrease in plasma aldosterone concentration. Serum potassium levels are not significantly affected by irbesartan alone at the recommended doses in patients without risk of electrolyte imbalance (Refer Special warnings and precautions for use and Interaction with other medicinal products and other forms of interaction section). Irbesartan does not inhibit ACE (kininase-II), an enzyme which generates angiotensin-II and also degrades bradykinin into inactive metabolites. Irbesartan does not require metabolic activation for its activity.

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

The combination of hydrochlorothiazide and irbesartan produces dose related additive reductions in blood pressure across their therapeutic dose ranges.

The blood pressure lowering effect of irbesartan in combination with hydrochlorothiazide is apparent after the first dose and substantially present within 1-2 weeks, with the maximal effect occurring by 6-8 weeks. In longterm, the effect of irbesartan/hydrochlorothiazide was maintained for over one year.

The long term treatment with hydrochlorothiazide reduces the risk of cardiovascular mortality and morbidity.

There is no difference in response to Irbesartan and Hydrochlorothiazide, regardless of age or gender. As is the case with other medicinal products that affect the renin-angiotensin system, black hypertensive patients have notably less response to irbesartan monotherapy. When irbesartan is administered concomitantly with a low dose of hydrochlorothiazide (e.g. 12.5 mg daily), the antihypertensive response in black patients approaches that of non-black patients.

Non-melanoma skin cancer:

Based on available data from epidemiological studies, cumulative dosedependent

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

5.2 Pharmacokinetic properties

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

Irbesartan and hydrochlorothiazide are orally active agents and do notrequire biotransformation for their activity. Following oral administration of Irbesartan and Hydrochlorothiazide, the absolute oral bioavailability is 60-80% and 50-80% for irbesartan and hydrochlorothiazide, respectively.

Food does not affect the bioavailability of Irbesartan and Hydrochlorothiazide. Peak plasma concentration occurs at 1.5-2 hours after oral administration for irbesartan and 1-5 hours for hydrochlorothiazide.

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

Irbesartan exhibits linear and dose proportional pharmacokinetics over the dose range of 10 to 600 mg. A less than proportional increase in oral absorption at doses beyond 600 mg was observed; the mechanism for this is unknown. The total body and renal clearance are 157-176 and 3.0-3.5 ml/min, respectively. The terminal elimination half-life of irbesartan is 11-15 hours. Steady-state plasma concentrations are attained within 3 days after initiation of a once-daily dosing regimen. However, there was no difference in the half-life and accumulation of irbesartan. No dosage adjustment is necessary in female patients. Irbesartan AUC and Cmax values were also somewhat greater in elderly subjects (> 65 years) than those of young subjects (18-40 years). However the terminal half-life was not significantly altered. No dosage adjustment is necessary in elderly patients. The mean plasma half-life of hydrochlorothiazide reportedly ranges from 5-15 hours.

Following oral or intravenous administration of 14C irbesartan, 80-85% of the circulating plasma radioactivity is attributable to unchanged irbesartan.

Irbesartan is metabolised by the liver via glucuronide conjugation and oxidation. The major circulating metabolite is irbesartan glucuronide (approximately 6%). In vitro studies indicate that irbesartan is primarily oxidised by the cytochrome P450 enzyme CYP2C9; isoenzyme CYP3A4 has negligible effect. Irbesartan and its metabolites are eliminated by both biliary and renal pathways. After either oral or intravenous administration of 14C irbesartan, about 20% of the radioactivity is recovered in the urine, and the remainder in the faeces. Less than 2% of the dose is excreted in the urine as unchanged irbesartan. Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidneys. At least 61% of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier, and is excreted in breast milk.

Renal impairment: in patients with renal impairment or those undergoing haemodialysis, the pharmacokinetic parameters of irbesartan are not significantly altered. Irbesartan is not removed by haemodialysis. In patients with creatinine clearance < 20 ml/min, the elimination half-life of hydrochlorothiazide was reported to increase to 21 hours.

Hepatic impairment: in patients with mild to moderate cirrhosis, the pharmacokinetic parameters of irbesartan are not significantly altered.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate, Sodium starch glycolate(Type A), Povidone, Silica

colloidal anhydrous, Talc, Sodium stearyl fumarate.

Film-coating:

Opadry II Pink 32F84835

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer outer package for expiry date.

Special precautions for storage

Store below 30°C.

Dosage Form and packaging available

Blister of 7 tablets.

7. MARKETING AUTHORISATION HOLDER

AUROBINDO

Aurobindo Pharma Ltd.,
Unit III, Survey No. 313 & 314,
Bachupally, Bachupally Mandal,
Medchal-Malkajgiri District,
Telangana State, India.

Regd. Office: Plot No.: 2, Maitrivihar,
Ameerpet, Hyderabad-500 038,
Telangana State, India.

8. Product Registration Holder in Malaysia:

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9. DATE OF REVISION OF THE TEXT

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