

SM PHARMACEUTICALS SDN BHD

IRBISAT 150 MG TABLETS IRBISAT 300 MG TABLETS

DESCRIPTION

Irbesat 150 MG:

White to off-white, oval shaped, film coated tablets, plain on one side and "I2" on the other side.

Irbesat 300 MG:

White to off-white, oval shaped, film coated tablets, plain on one side and "I3" on the other side.

COMPOSITION:

Irbesat 150 MG

Each tablet contains: Irbesartan 150 mg

Irbesat 300 MG:

Each tablet contains: Irbesartan 300 mg

PHARMACOLOGICAL PROPERTIES: PHARMACODYNAMICS:

Mechanism of action

Irbesartan is a potent, orally active, selective angiotensin-II receptor (type AT1) 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. 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.

Clinical Efficacy

Hypertension

Irbesartan lowers blood pressure with minimal change in heart rate. The decrease in blood pressure is dose-related for once a day doses with a tendency towards plateau at doses above 300 mg. Doses of 150-300 mg once daily lower supine or seated blood pressures at trough (i.e. 24 hours after dosing) by an average of 8-13/5-8 mm Hg (systolic/diastolic) greater than those associated with placebo.

Peak reduction of blood pressure is achieved within 3-6 hours after administration and the blood pressure lowering effect is maintained for at least 24 hours. At 24 hours the reduction of blood pressure was 60-70% of the corresponding peak diastolic and systolic responses at the recommended doses. Once-daily dosing with 150 mg produced trough and mean 24 hour responses similar to twice daily dosing on the same total dose.

The blood pressure lowering effect of Irbesartan is evident within 1-2 weeks, with the maximal effect occurring by 4-6 weeks after start of therapy. The antihypertensive effects are maintained during long term therapy. After withdrawal of therapy, blood pressure gradually returns toward baseline. Rebound hypertension has not been observed.

The blood pressure lowering effects of irbesartan and thiazide-type diuretics are additive. In patients not adequately controlled by irbesartan alone, the addition of a low dose of hydrochlorothiazide (12.5 mg) to irbesartan once daily results in a further placebo-adjusted blood pressure reduction at trough of 7-10/3-6 mm Hg (systolic/diastolic).

Hypertension and type-2 diabetes with renal disease

Irbesartan decreases the progression of renal disease in patients with chronic renal insufficiency and overt proteinuria. Irbesartan 300 mg delays progression to overt proteinuria in patients with micro albuminuria.

PHARMACOKINETICS:

Absorption

After oral administration, irbesartan is well absorbed. Concomitant food intake does not significantly influence the bioavailability of irbesartan.

Distribution

Plasma protein binding is approximately 96%, with negligible binding to cellular blood components. The volume of distribution is 53 - 93 litres.

Metabolism

Irbesartan is metabolised by the liver via glucuronide conjugation and oxidation. The major circulating metabolite is irbesartan glucuronide (approximately 6%). Irbesartan is primarily oxidised by the cytochrome P450 enzyme CYP2C9; isoenzyme CYP3A4 has negligible effect.

Linearity/non-linearity

Irbesartan exhibits linear and dose proportional pharmacokinetics over the dose range of 10 to 600 mg. A less than proportional increase in oral absorption at doses beyond 600 mg (twice the maximal recommended dose) was observed; the mechanism for this is unknown. Peak plasma concentrations are attained at 1.5 to 2.0 hours after oral administration. The total body and renal clearance are 157-176 and 3 - 3.5 ml / min respectively. The terminal elimination half-life of irbesartan is 11 - 15 hours. Steady state plasma concentrations are attained within 3 days after initiation of a once-daily dosing regimen. Limited accumulation of irbesartan (<20%) is observed in plasma upon repeated once-daily dosing.

Elimination

Irbesartan and its metabolites are eliminated by both biliary and renal pathways. Less than 2% of dose is excreted in the urine as unchanged irbesartan.

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.

Hepatic impairment

In patients with mild to moderate cirrhosis, the pharmacokinetic parameters of irbesartan are not significantly altered. Studies have not been performed in patients with severe hepatic impairment.

INDICATIONS:

Treatment of essential hypertension.

Treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (>300 mg/day) in patients with type 2 diabetes and hypertension.

In this population, Irbesartan reduces the rate of progression of nephropathy as measured by the occurrence of doubling of serum creatinine or end-stage renal disease (need for dialysis or renal transplantation).

CONTRAINDICATIONS:

° Hypersensitivity to the active substance or to any of the excipients

° Second and third trimesters of pregnancy.

° The concomitant use of Irbesartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (glomerular filtration rate (GFR) <60 ml/min/1.73m2).

SIDE EFFECTS / ADVERSE REACTIONS:

Undesirable effects:

In placebo-controlled trials in patients with hypertension, the overall incidence of adverse events did not differ between the irbesartan (56.2%) and the placebo groups (56.5%). Discontinuation due to any clinical or laboratory adverse event was less frequent for irbesartan-treated patients (3.3%) than for placebo-treated patients (4.5%). The incidence of adverse events was not related to dose (in the recommended dose range), gender, age, race, or duration of treatment.

In diabetic hypertensive patients with microalbuminuria and normal renal function, orthostatic dizziness and orthostatic hypotension were reported in 0.5% of the patients (i.e., uncommon) but in excess of placebo.

The following table presents the adverse drug reactions that were reported in placebo-controlled trials in which 1,965 hypertensive patients received irbesartan. Terms marked with a star (*) refer to the adverse reactions that were additionally reported in > 2% of diabetic hypertensive patients with chronic renal insufficiency and overt proteinuria and in excess of placebo.

The frequency of adverse reactions listed below is defined using the following convention:

Very common (≥ 1/10);

Common (≥ 1/100 to < 1/10);

Uncommon (≥ 1/1,000 to < 1/100);

Rare (≥ 1/10,000 to < 1/1,000);

Very rare (< 1/10,000)

Adverse reactions additionally reported are also listed. These adverse reactions are derived from spontaneous reports.

Blood and lymphatic system disorders	
Not known	Anaemia, Thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity reactions such as angioedema, rash, urticaria, anaphylactic reaction, anaphylactic shock
Metabolism and nutrition disorders	
Not known	Hyperkalemia, Hypoglycaemia
Nervous system disorders	
Common	Dizziness, Orthostatic dizziness
Not known	Vertigo, headache
Ear and labyrinth disorder	
Not known	Tinnitus
Cardiac disorders	
Uncommon	Tachycardia

Vascular disorders	
Common	Orthostatic hypotension*
Uncommon	Flushing
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough
Gastrointestinal disorders	
Common	Nausea/vomiting
Uncommon	Diarrhoea, dyspepsia/ heartburn
Not known	Dysgeusia
Hepatobiliary Disorders	
Uncommon	Jaundice
Not known	Hepatitis, Abnormal liver function
Skin and Subcutaneous tissue disorders	
Not known	Leukocytoclastic vasculitis
Musculoskeletal and connective tissue disorders	
Common	Musculoskeletal pain*
Not known	Arthralgia, myalgia (in some cases associated with increased plasma creatine kinase levels), muscle cramps
Renal and urinary disorders	
Not known:	Impaired renal function including cases of renal failure in patients at risk
Reproductive system and breast disorders	
Uncommon:	Sexual dysfunction
General disorders and administration site conditions	
Common:	Fatigue
Uncommon:	Chest pain

Investigations:

Very common: Hyperkalaemia* occurred more often in diabetic patients treated with irbesartan than with placebo. In diabetic hypertensive patients with microalbuminuria and normal renal function, hyperkalaemia (≥ 5.5 mEq/L) occurred in 29.4% of the patients in the irbesartan 300 mg group and 22% of the patients in the placebo group. In diabetic hypertensive patients with chronic renal insufficiency and overt proteinuria, hyperkalaemia (≥ 5.5 mEq/L) occurred in 46.3% of the patients in the irbesartan group and 26.3% of the patients in the placebo group.

Common: significant increases in plasma creatine kinase were commonly observed (1.7%) in irbesartan treated subjects. None of these increases were associated with identifiable clinical musculoskeletal events. In 1.7% of hypertensive patients with advanced diabetic renal disease treated with irbesartan, a decrease in haemoglobin*, which was not clinically significant, has been observed.

Paediatric population:

In a randomised trial of 318 hypertensive children and adolescents aged 6 to 16 years, the following adverse reactions occurred in the 3-week double-blind phase: headache (7.9%), hypotension (2.2%), dizziness (1.9%), cough (0.9%). In the 26-week open-label period of this trial the most frequent laboratory abnormalities observed were creatinine increases (6.5%) and elevated CK values in 2% of child recipients.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

PRECAUTIONS / WARNINGS:

Intravascular volume depletion:

Symptomatic hypotension, especially after the first dose, may 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 the administration of Irbesartan.

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 medicinal products that affect the renin-angiotensin-aldosterone system. While this is not documented with Irbesartan, a similar effect should be anticipated with angiotensin-II receptor antagonists.

Renal impairment and kidney transplantation:

When irbesartan is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of irbesartan in patients with recent kidney transplantation.

Hypertensive patients with type 2 diabetes and renal disease:

The effects of irbesartan both on renal and cardiovascular events were not uniform across all subgroups, in an analysis carried out in the study with patients with advanced renal disease. In particular, they appeared less favourable in women and non-white subjects.

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

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Hyperkalemia:

As with other medicinal products that affect the renin - angiotensin - aldosterone system, hyperkalemia may occur during the treatment with Irbesartan, especially in the presence of renal impairment, overt proteinuria due to diabetic renal disease, and/or heart failure. Close monitoring of serum potassium in patients at risk is recommended.

Hypoglycaemia:

Irbesartan may induce hypoglycaemia, particularly in diabetic patients. In patients treated with insulin or antidiabetics an appropriate blood glucose monitoring should be considered; a dose

adjustment of insulin or antidiabetics may be required when indicated

Lithium:

The combination of lithium and Irbesartan is not recommended

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy:

As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Primary aldosteronism:

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

General:

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

As observed for angiotensin converting enzyme inhibitors, irbesartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

Pregnancy:

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

Paediatric population:

Irbesartan has been studied in paediatric populations aged 6 to 16 years old but the current data are insufficient to support an extension of the use in children until further data become available.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE:

Based on its Pharmacodynamic properties, Irbesartan is unlikely to affect the ability to drive and use machines. When driving vehicles or operating machines, it should be taken into account that dizziness or weariness may occur during treatment.

Instructions for use:

For oral use. Can be taken with or without food.

DRUG INTERACTIONS:

Diuretics and other antihypertensive agents:

Other antihypertensive agents may increase the hypotensive effects of irbesartan; however, Irbesartan has been safely administered with other antihypertensive agents, such as beta-blockers,

long-acting calcium channel blockers, and thiazide diuretics. Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with Irbesartan.

Aliskiren-containing products and ACE-inhibitors:

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

Potassium supplements and potassium-sparing diuretics:

Based on experience with the use of other medicinal products 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 serum potassium levels (e.g. heparin) may lead to increases in serum potassium and is, therefore, not recommended.

Lithium:

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Similar effects have been very rarely reported with irbesartan so far. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Non-steroidal anti-inflammatory drugs:

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

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

Repaglinide:

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

Additional information on irbesartan interactions:

The pharmacokinetic of irbesartan is not affected by hydrochlorothiazide. Irbesartan is mainly metabolised by CYP2C9 and to a lesser extent by glucuronidation. No significant pharmacokinetic or pharmacodynamic interactions were observed when irbesartan was coadministered with warfarin, a medicinal product metabolised by CYP2C9. The effects of CYP2C9 inducers such as rifampicin on

the pharmacokinetic of irbesartan have not been evaluated. The pharmacokinetic of digoxin was not altered by coadministration of irbesartan.

PREGNANCY AND LACTATION

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

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

• 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.

Breast-feeding:

Because no information is available regarding the use of Irbesartan during breast-feeding, it is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant. It is unknown whether irbesartan or its metabolites are excreted in human milk.

Fertility:

Irbesartan had no effect upon fertility of treated rats and their offspring up to the dose levels inducing the first signs of parental toxicity

ROUTE OF ADMINISTRATION:

Oral (Solid Dosage Form)

RECOMMENDED DOSAGE, DOSAGE SCHEDULE AND ROUTE OF ADMINISTRATION:

Posology:

The usual recommended initial and maintenance dose is 150mg once daily, with or without food. Irbesartan at a dose of 150 mg once daily generally provides a better 24 hour blood pressure control than 75mg. However, initiation of therapy with 75 mg could be considered, particularly in haemodialysed patients and in the elderly over 75 years.

In patients insufficiently controlled with 150 mg once daily, the dose of Irbesartan can be increased to 300 mg, or other antihypertensive agents can be added. In particular, the addition of a diuretic such as hydrochlorothiazide has been shown to have an additive effect with Irbesartan.

In hypertensive type 2 diabetic patients, therapy should be initiated at 150 mg Irbesartan once daily and titrated up to 300 mg once daily as the preferred maintenance dose for treatment of renal disease. The demonstration of renal benefit of Irbesartan in hypertensive type 2 diabetic patients is based on studies where Irbesartan was used in addition to other antihypertensive agents, as needed, to reach target blood pressure.

Special Populations

Renal impairment:

No dosage adjustment is necessary in patients with impaired renal function. A lower starting dose (75 mg) should be considered for patients undergoing hemodialysis. If a lower starting dose is considered necessary, the 150 mg tablet not being breakable, alternative therapy should be considered.

Hepatic impairment:

No dosage adjustment is necessary in patients with mild to moderate hepatic impairment. There is no clinical experience in patients with severe hepatic impairment.

Elderly patients:

Although consideration should be given to initiating therapy with 75 mg in patients over 75 years of age, dosage adjustment is not usually necessary for patients over 75 years of age. If a lower starting dose is considered necessary, the 150 mg tablet not being breakable, alternative therapy should be considered.

Paediatric population:

The safety and efficacy of Irbesartan in children aged 0 to 18 years has not been established.

SYMPTOMS AND TREATMENT FOR OVERDOSE AND ANTIDOTE(S):

Experience in adults exposed to doses of up to 900 mg/day for 8 weeks revealed no toxicity. The most likely manifestations of overdose are expected to be hypotension and tachycardia; bradycardia might also occur from overdose. No specific information is available on the treatment of overdose with Irbesartan. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Suggested measures include induction of emesis and/or gastric lavage. Activated charcoal may be useful in the treatment of overdose. Irbesartan is not removed by haemodialysis.

PACKING / PACK SIZES:

2 x 14's (28 Tablets).

STORAGE CONDITIONS, USER INSTRUCTIONS AND PHARMACEUTICAL PRECAUTIONS:

Store below 30°C.

SHELF LIFE:

3 years

MANUFACTURER AND PRODUCT REGISTRATION HOLDER:

SM PHARMACEUTICALS SDN BHD (218620-M)

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