180mm

250mm

ARBI® Tablet

آربی گولیاں

(Irbesartan USP)

COMPOSITION
Arbi® 150 mg tablet
Each film coated tablet contains:
Irbesartan USP……..150 mg
Arbi® 300 mg tablet
Each film coated tablet contains:
Irbesartan USP……..300 mg
(BP specs.)

WARNING: FETAL TOXICITY
When pregnancy is detected, discontinue Irbesartan as soon as possible. Drugs that act directly on the renin -angiotensin system can cause injury and death to the developing fetus.

DESCRIPTION
Irbesartan is an angiotensin II receptor (AT1 subtype) antagonist. Irbesartan is a non-peptide compound, chemically described as a 2-butyl-3-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en 4 one. Its empirical formula is $C_{25}H_{28}N_6O$ and molecular weight is 428.5.

CLINICAL PHARMACOLOGY

Pharmacodynamics
In healthy subjects, single oral irbesartan doses of up to 300 mg produced dose-dependent inhibition of the pressor effect of angiotensin II infusions. Inhibition was complete (100%) 4 hours following oral doses of 150 mg or 300 mg and partial inhibition was sustained for 24 hours (60% and 40% at 300 mg and 150 mg, respectively). In hypertensive patients, angiotensin II receptor inhibition following chronic administration of irbesartan causes a 1.5-fold to 2-fold rise in angiotensin II plasma concentration and a 2-fold to 3-fold increase in plasma renin levels. Aldosterone plasma concentrations generally decline following irbesartan administration, but serum potassium levels are not significantly affected at recommended doses. In hypertensive patients, chronic oral doses of irbesartan (up to 300 mg) had no effect on glomerular filtration rate, renal plasma flow, or filtration fraction. In multiple dose studies in hypertensive patients, there were no clinically important effects on fasting triglycerides, total cholesterol, HDL-cholesterol, or fasting glucose concentrations. There was no effect on serum uric acid during chronic oral administration, and no uricosuric effect.

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.

Pharmacokinetics

Absorption
Irbesartan is an orally active agent that does not require biotransformation into an active form. The oral absorption of irbesartan is rapid and complete with an average absolute bioavailability of 60% to 80%. Concomitant food intake does not significantly influence the bioavailability of irbesartan.

Distribution
Irbesartan is 90% bound to serum proteins (primarily albumin and α1-acid glycoprotein) with negligible binding to cellular components of blood. The average volume of distribution is 53 to 93 liters.

Metabolism
Irbesartan is an orally active agent that does not require biotransformation into an active form. Irbesartan is metabolized via glucuronide conjugation and oxidation. Following oral or intravenous administration of 14C- labeled irbesartan, more than 80% of the circulating plasma radioactivity is attributable to unchanged irbesartan. The primary circulating metabolite is the inactive irbesartan glucuronide conjugate (approximately 6%).
In vitro studies indicate irbesartan is oxidized primarily by CYP2C9; metabolism by CYP3A4 is negligible.

Elimination
Total plasma and renal clearances of Irbesartan are in the range of 157 to 176 mL/min and 3.0 to 3.5 mL/min, respectively. The terminal elimination half-life of Irbesartan averages 11 to 15 hours. Steady-state concentrations are achieved within 3 days. Irbesartan and its metabolites are eliminated by both biliary and renal pathways. After either oral or IV 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.

INDICATIONS
• Arbi is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure lowers the risk of fatal and non-fatal cardiovascular (CV) events, primarily strokes and myocardial infarction. It may be used alone or in combination with other antihypertensive agents.

• Arbi is indicated for the treatment of diabetic nephropathy in patients with type 2 diabetes and hypertension, an elevated serum creatinine, and proteinuria (>300 mg/day). 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)

DOSAGE AND ADMINISTRATION

General considerations
Arbi may be administered with other antihypertensive agents and with or without food.

Hypertension
The recommended initial dose of Arbi is 150 mg once daily. The dosage can be increased to a maximum dose of 300 mg once daily as needed to control blood pressure. In particular, the addition of a diuretic such as hydrochlorothiazide has been shown to have an additive effect with Irbesartan.

Nephropathy in type 2 diabetic patients
The recommended dose is 300 mg once daily. Therapy may also be initiated with 150 mg and then titrated to 300 mg in these patients.

Dosing consideration in special populations

Renal Impairment
The pharmacokinetics of irbesartan were not altered in patients with renal impairment or in patients on hemodialysis. Irbesartan is not removed by hemodialysis No dosage adjustment is necessary in patients with impaired renal function. A lower starting dose (75 mg) should be considered for patients undergoing haemodialysis.

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.

Administration requirements
Irbesartan may be administered with other antihypertensive agents and with or without food.

CONTRAINDICATIONS
• Irbesartan is contraindicated in patients who are hypersensitive to component of this product
• When pregnancy is detected, irbesartan should be discontinued as soon as possible.
• 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/1.73 m^2)

WARNINGS AND PRECAUTIONS

Fetal Toxicity
Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. When pregnancy is diagnosed, treatment with irbesartan should be stopped immediately, and, if appropriate, alternative therapy should be started.

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, diarrhea or vomiting. Correct volume or salt depletion prior to administration of Irbesartan or use a lower starting dose.

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 drugs that affect the renin-angiotensin-aldosterone system.

Impaired Renal Function
Changes in renal function including acute hypotension, azotemia, oliguria or rarely acute renal failure can be caused by drugs that inhibit the renin-angiotensin system. Patients whose renal function may depend in part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, chronic kidney disease, severe heart failure, or volume depletion) may be at risk of developing acute renal failure or death on Irbesartan. Renal function should be monitored periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function.
When Irbesartan is used in patients with existing impairment of renal function, a periodic monitoring of potassium and creatinine serum levels is recommended.

Kidney transplantation
There is no experience regarding the administration of Irbesartan in patients with recent kidney transplantation.

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

Hyperkalemia
As with other drugs 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.

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 drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of

180mm

250mm

Irbesartan is not recommended.
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 pharmacodynamics properties, Irbesartan is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that dizziness or weariness may occur during treatment.

ADVERSE REACTIONS
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).

Immune system disorders
*Not known:*hypersensitivity reactions such as angioedema, rash, urticaria
Nervous system disorders
*Common:*dizziness, orthostatic dizziness*
*Not known:*vertigo, headache
Ear and labyrinth disorders
*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.

* 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.

DRUG INTERACTIONS

Agents increasing serum potassium level
Coadministration of Irbesartan with other drugs that raise serum potassium levels (potassium supplements, salt substitutes containing potassium, potassium sparing diuretics, heparin) may result in hyperkalemia, sometimes severe. Monitor serum potassium in such patients.

Lithium
Increases in serum lithium concentrations and lithium toxicity have been reported with concomitant use of Irbesartan and lithium. Monitor lithium levels in patients receiving Irbesartan and lithium.

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 or volume depletion (such as patients on diuretic therapy). 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.

Dual Blockade of the Renin-Angiotensin System (RAS)
Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Most patients receiving the combination of two RAS inhibitors do not obtain any additional benefit compared to monotherapy. In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function and electrolytes in patients on Irbesartan and other agents that affect the RAS.
Do not co-administer aliskiren with Irbesartan in patients with diabetes and in patients with renal impairment (creatinine clearance <60 mL/min).

USE IN SPECIAL POPULATIONS

Pregnancy Category
US FDA pregnancy category D. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is diagnosed, treatment with Irbesartan should be stopped immediately, and, if appropriate, alternative therapy should be started. Irbesartan use is not recommended during the first trimester of pregnancy and is contraindicated in the second and third trimesters of pregnancy.
If exposure to Irbesartan has occurred during pregnancy, fetal testing must be performed. Ultrasound check of renal function and skull is recommended. Serial ultrasound examinations are recommended to assess the intra-amniotic environment. Patients and physicians should be aware however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.
Infants whose mothers have taken AIIRAs should be closely observed for hypotension, oliguria and hypokalemia.

Nursing mothers
Because no information is available regarding the use of Irbesartan during breast-feeding, Irbesartan 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.

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

Renal impairment
No dosage adjustment is necessary in patients with mild to severe renal impairment unless a patient with renal impairment is also volume depleted (see DOSAGE AND ADMINISTRATION)

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. (See DOSAGE AND ADMINISTRATION)

Geriatrics
In elderly subjects (age 65-80 years), Irbesartan elimination half-life is not significantly altered, but AUC and Amax values are about 20% to 50% greater than those of young subjects (age 18-40 years). No dosage adjustment is necessary in the elderly.

OVERDOSAGE
No data are available concerning over dosage in humans. However, daily doses of 900 mg for 8 weeks were well-tolerated. The most likely manifestations of over dosage 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.

PRESENTATION
ARBI® 150mg is available in pack of 10 tablets.
ARBI® 300mg is available in pack of 10 tablets.

INSTRUCTIONS
Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 30°C.
For suspected adverse drug reaction, email us at reports@pharmevo.biz

For more information on our products call PharmAssist helpline 0800-82222 Monday to Friday 9:00 am to 6:00 pm or email us at : pharmassist@pharmevo.biz

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