BESART

(Irbesartan)

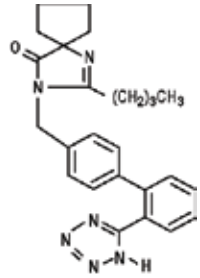
Tablets

150 mg & 300 mg

بِسارٹ گولیاں

DESCRIPTION

BESART (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 the structural formula:



QUALITATIVE & QUANTITATIVE COMPOSITION

BESART (irbesartan) is available for oral administration as:

1. BESART 150 mg Tablet

Each film coated tablet contains

Irbesartan……150 mg

2. BESART 300 mg Tablet

Each film coated tablet contains

Irbesartan……300 mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Angiotensin II is a potent vasoconstrictor formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the primary vasoactive hormone of the renin-angiotensin system, and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Irbesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively binding to the AT1 angiotensin II receptor found in many tissues (e.g., vascular smooth muscle, adrenal gland). There is also an AT2 receptor in many tissues, but it is not involved in cardiovascular homeostasis.

Irbesartan is a specific competitive antagonist of AT1 receptors with a much greater affinity (more than 8500-fold) for the AT1 receptor than for the AT2 receptor and no agonist activity. Blockade of the AT1 receptor removes the negative feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and circulating angiotensin II do not overcome the effects of irbesartan on blood pressure.

Irbesartan does not inhibit ACE or renin or affect other hormone receptors or ion channels known to be involved in the cardiovascular regulation of blood pressure and sodium homeostasis.

Pharmacodynamics

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.

Pharmacokinetics

Absorption

The oral absorption of irbesartan is rapid and complete with an average absolute bioavailability of 60% to 80%. Following oral administration of **BESART**, peak plasma concentrations of irbesartan are attained at 1.5 to 2 hours after dosing. Food does not affect the bioavailability of irbesartan. Irbesartan exhibits linear pharmacokinetics over the therapeutic dose range.

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.

Elimination

Total plasma and renal clearances 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. Steadystate concentrations are achieved within 3 days. Limited accumulation of irbesartan (<20%) is observed in plasma upon repeated once daily dosing and is not clinically relevant.

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%). The remaining oxidative metabolites do not add appreciably to irbesartan's pharmacologic activity.

Irbesartan and its metabolites are excreted by both biliary and renal routes.

SPECIAL POPULATION

Sex

No sex-related differences in pharmacokinetics are observed in healthy elderly (age 65-80 years) or in healthy young (age 18-40 years) subjects.

Geriatrics

No dosage adjustment is necessary in the elderly.

Race/Ethnicity

In healthy black subjects, irbesartan AUC values are approximately 25% greater than whites; there is no difference in Cmax values.

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.

Hepatic Insufficiency
No dosage adjustment is necessary in patients with hepatic insufficiency.

THERAPEUTIC INDICATIONS
BESART is an angiotensin II receptor blocker (ARB) indicated for:
Treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.
Treatment of diabetic nephropathy in hypertensive patients with type 2 diabetes, an elevated serum creatinine, and proteinuria.

DOSAGE & ADMINISTRATION
General Considerations
BESART may be administered with other antihypertensive agents and with or without food.

Hypertension
The recommended initial dose of **BESART** 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.

Nephropathy in Type 2 Diabetic Patients
The recommended dose is 300 mg once daily.

Dose Adjustment in Volume and Salt-Depleted Patients
The recommended initial dose is 75 mg once daily in patients with depletion of intravascular volume or salt (e.g., patients treated vigorously with diuretics or on hemodialysis).

ADVERSE EFFECTS
Nephropathy in type 2 diabetic patients: The most common adverse reactions which were more frequent than placebo were hyperkalemia dizziness, orthostatic dizziness, and orthostatic hypotension.

CONTRAINDICATIONS
BESART is contraindicated in patients who are hypersensitive to any component of this product.
Do not coadminister aliskiren with **BESART** in patients with diabetes.

OVERDOSAGE
No data are available in regard to overdosage in humans. However, daily doses of 900 mg for 8 weeks were well-tolerated. The most likely manifestations of overdosage are expected to be hypotension and tachycardia; bradycardia might also occur from overdose. Irbesartan is not removed by hemodialysis. Acute oral toxicity studies with irbesartan in mice and rats indicated acute lethal doses were in excess of 2000 mg/kg, about 25-fold and 50-fold the MRHD (300 mg) on a mg/m2 basis, respectively.

WARNINGS AND PRECAUTIONS
- Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue **BESART** as soon as possible.
- In patients with an activated renin-angiotensin system, such as volume or salt-depleted patients (e.g. those being treated with high doses of diuretics), symptomatic hypotension may occur after initialization of treatment with **BESART**. Correct volume or salt depletion prior to administration of **BESART** or use a lower starting dose.
- Changes in renal function including 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 particular risk of developing acute renal failure or death on **BESART**. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on **BESART**.

DRUG INTERACTIONS
- Lithium: Risk of lithium toxicity.
- Non-Steroidal Anti-inflammatory Drugs (NSAIDs) and COX-2 inhibitors: Increased risk of renal impairment. Reduced antihypertensive effects.
- Dual blockade of the renin-angiotensin system: Increased risk of renal impairment, hypotension, and hyperkalemia.

STORAGE
Store at 25°C (Excursions permitted between 15°C to 30°C).
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
BESART (Irbesartan) 150mg tablets are available in blister pack of 10's.
BESART (Irbesartan) 300mg tablets are available in blister pack of 10's.

Keep out of reach of children

To be sold on prescription of a registered medical Practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

ہدایات:
دوا کو ۲۵ ڈگری سینٹی گریڈ درجہ حرارت پر رکھیں۔
(درجہ حرارت کی حد ۱۵ سے ۳۰ ڈگری سینٹی گریڈ ہے)
دھوپ اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

Manufactured by:
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