BESART - PLUS

(Irbesartan + Hydrochlorothiazide)

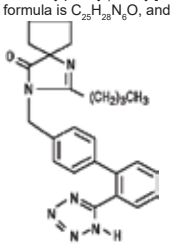
Tablets

150 mg + 12.5 mg & 300 mg + 12.5 mg

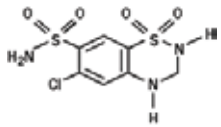
بسارٹ پلس گولیاں

DESCRIPTION

BESART-PLUS (irbesartan-hydrochlorothiazide) tablets are a combination of an angiotensin II receptor antagonist (AT1 subtype), irbesartan, and a thiazide diuretic, hydrochlorothiazide (HCTZ). 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 its structural formula is:



Hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7 -sulfonamide 1,1¬ dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$ and its structural formula is:



QUALITATIVE & QUANTITATIVE COMPOSITION

BESART-PLUS (Irbesartan + Hydrochlorothiazide) is available for oral administration as:

1. BESART-PLUS 150 mg + 12.5 mg Tablet

Each film coated tablet contains

Irbesartan……..150 mg

Hydrochlorothiazide……12.5 mg

2. BESART-PLUS 300 mg + 12.5 mg Tablet

Each film coated tablet contains

Irbesartan……..300 mg

Hydrochlorothiazide……12.5 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.

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

Pharmacodynamics

Irbesartan

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.

Hydrochlorothiazide

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

Pharmacokinetics

Absorption

Irbesartan

The oral absorption of irbesartan is rapid and complete with an average absolute bioavailability of 60% to 80%. Following oral administration of AVAPRO, 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.

Hydrochlorothiazide

When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours.

Distribution

Irbesartan

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.

Hydrochlorothiazide

Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

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

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.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated unchanged within 24 hours.

SPECIAL POPULATION

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. When pregnancy is detected, discontinue **BESART-PLUS** as soon as possible.

Nursing Mothers
Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

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-PLUS is a combination of irbesartan, an angiotensin II receptor antagonist, and hydrochlorothiazide, a thiazide diuretic, indicated for hypertension:
In patients not adequately controlled with monotherapy.
As initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals.

DOSAGE & ADMINISTRATION
General Considerations
The side effects of irbesartan are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent (primarily hypokalemia) and dose independent phenomena (e.g., pancreatitis), the former much more common than the latter.
Maximum antihypertensive effects are attained within 2 to 4 weeks after a change in dose.
BESART-PLUS may be administered with or without food.
BESART-PLUS may be administered with other antihypertensive agents.

Renal Impairment
The usual regimens of therapy with **BESART-PLUS** may be followed as long as the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so **BESART-PLUS** is not recommended.

Hepatic Impairment
No dosage adjustment is necessary in patients with hepatic impairment.

Add-On Therapy
In patients not controlled on monotherapy with irbesartan or hydrochlorothiazide, the recommended doses of **BESART-PLUS**, in order of increasing mean effect, are (irbesartanhydrochlorothiazide) 150/12.5 mg, 300/12.5 mg, and 300/25 mg. The largest incremental effect will likely be in the transition from monotherapy to 150/12.5 mg.

Replacement Therapy
BESART-PLUS may be substituted for the titrated components.

Initial Therapy
The usual starting dose is **BESART-PLUS** 150/12.5 mg once daily. The dosage can be increased after 1 to 2 weeks of therapy to a maximum of 300/25 mg once daily as needed to control blood pressure. **BESART-PLUS** is not recommended as initial therapy in patients with intravascular volume depletion.

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-PLUS** is contraindicated in patients who are hypersensitive to any component of this product.
- Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.
- Do not coadminister aliskiren with **BESART-PLUS** in patients with diabetes.

OVERDOSAGE
Irbesartan
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.

Hydrochlorothiazide
The most common signs and symptoms of overdose observed in humans are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The oral LD50 of hydrochlorothiazide is greater than 10 g/kg in both mice and rats

WARNINGS AND PRECAUTIONS
- Pregnancy Category D. When pregnancy is detected, discontinue **BESART-PLUS** as soon as possible.
- Hypotension: Correct volume depletion prior to administration.
- Impaired renal function.
- Thiazide diuretics may cause an exacerbation or activation of systemic lupus erythematosus.
- Secondary acute angle-closure glaucoma and/or acute myopia.

DRUG INTERACTIONS
- NSAIDs and selective COX-2 inhibitors: Can reduce diuretic, natriuretic of diuretic, may lead to increased risk of renal impairment and reduced antihypertensive effect. Monitor renal function periodically.
- Dual blockade of the renin-angiotensin system: Increased risk of renal impairment, hypotension, and hyperkalemia.
- Antidiabetic drugs: Dosage adjustment of antidiabetic may be required.
- Cholestyramine and colestipol: Reduced absorption of thiazides.
- Lithium: Increases in serum lithium concentrations and lithium toxicity.
- Carbamazepine: Increased risk of hyponatremia

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-PLUS (Irbesartan + Hydrochlorothiazide) 150 mg + 12.5 mg tablets are available in blister pack of 14's.
BESART-PLUS (Irbesartan + Hydrochlorothiazide) 300 mg + 12.5 mg 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۔

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SCILIFE

Manufactured by:
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