Covam® PLUS

کووام پلس

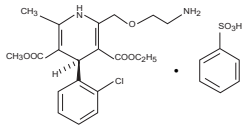
[Amlodipine+Valsartan+Hydrochlorothiazide]

Film-coated Tablets
5mg + 160mg + 12.5mg, 5mg + 160mg + 25mg, 10mg + 160mg + 12.5mg, 10mg + 160mg + 25mg, 10mg + 320mg + 25mg.

DESCRIPTION

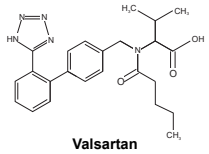
Covam Plus Tablet is a fixed dose combination of amlodipine, valsartan and hydrochlorothiazide.

Amlodipine:
Amlodipine is a calcium channel blocker (CCB). The chemical name of amlodipine is 3-Ethyl 5-methyl (±)-2- [(2-aminoethoxy) methyl]- 4-(o chlorophenyl)-1,4-dihydro-6-methyl-3,5 pyridinedicarboxylate, monobenzenesulfonate. Its molecular formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$ and structural formula is:



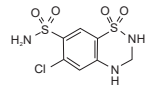
Amlodipine Besylate

Valsartan:
Valsartan is a non-peptide, orally active, and specific angiotensin II antagonist acting on the AT1 receptor subtype. Valsartan's chemical name is N-(1-oxopentyl)-N-[[2′-(1H-tetrazol-5-yl) [1,1′-biphenyl]-4-yl]methyl]-L-valine. Its molecular formula is $C_{24}H_{29}N_5O_3$ and structural formula is:



Valsartan

Hydrochlorothiazide:
Hydrochlorothiazide is a thiazide diuretic. Hydrochlorothiazide is chemically described as 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its molecular formula is $C_7H_8ClN_3O_4S_2$ and structural formula is:



Hydrochlorothiazide

QUALITATIVE AND QUANTITATIVE COMPOSITION

Covam Plus (Amlodipine + Valsartan + Hydrochlorothiazide) Tablets are available for oral administration as:

Covam Plus Tablets 5mg+160mg+12.5mg
Each film-coated tablet contains:
Amlodipine...5mg (as amlodipine besylate USP)
Valsartan USP...160mg
Hydrochlorothiazide USP...12.5mg

Covam Plus Tablets 5mg+160mg+25mg
Each film-coated tablet contains:
Amlodipine...5mg (as amlodipine besylate USP)
Valsartan USP...160mg
Hydrochlorothiazide USP...25mg

Covam Plus Tablets 10mg+160mg+12.5mg
Each film-coated tablet contains:
Amlodipine...10mg (as amlodipine besylate USP)
Valsartan USP...160mg
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Each film-coated tablet contains:
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Covam Plus Tablets 10mg+320mg+25mg
Each film-coated tablet contains:
Amlodipine...10mg (as amlodipine besylate USP)
Valsartan USP...320mg
Hydrochlorothiazide USP...25mg

CLINICAL PHARMACOLOGY

Mechanism of Action
The active ingredients of Covam Plus (Amlodipine + Valsartan + Hydrochlorothiazide) Tablets target three separate mechanisms involved in blood pressure regulation.

Amlodipine:
Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure. It is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Amlodipine binds to both dihydropyridine and nondihydropyridine binding sites.

Valsartan:
Valsartan is an orally active, potent and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. Angiotensin II is the principal presser agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

Hydrochlorothiazide:
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.

Pharmacokinetics
Amlodipine:
Peak plasma concentrations of amlodipine are reached 6 to 12 hours after administration of amlodipine alone. Absolute bioavailability has been estimated to be between 64% and 90%. The apparent volume of distribution of amlodipine is 21 L/kg. Approximately 93% of circulating amlodipine is bound to plasma proteins in hypertensive patients. Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. Elimination of amlodipine from the plasma is biphasic with a terminal elimination half-life of about 30 to 50 hours. Steady state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Valsartan:
Following oral administration of valsartan alone peak plasma concentrations of valsartan are reached in 2 to 4 hours. Absolute bioavailability is about 25% (range 10% to 35%). The steady state volume of distribution of valsartan after intravenous administration is 17 L indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (95%), mainly serum albumin. Valsartan shows biexponential decay kinetics following intravenous administration with an average elimination half-life of about 6 hours. The recovery is mainly as unchanged drug, with only about 20% of dose recovered as metabolites. The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan. Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance).

Hydrochlorothiazide:
The estimated absolute bioavailability of hydrochlorothiazide after oral administration is about 70%. Peak plasma hydrochlorothiazide concentrations (C_{max}) are reached within 2 to 5 hours after oral administration. Hydrochlorothiazide binds to albumin (40% to 70%) and distributes into erythrocytes. Following oral administration, plasma hydrochlorothiazide concentrations decline biexponentially, with a mean distribution half-life of about 2 hours and an elimination half-life of about 10 hours. About 70% of an orally administered dose of hydrochlorothiazide is eliminated in the urine as unchanged drug.

Special Population
Elderly population:
Elderly patients have decreased clearance of amlodipine with a resulting increase in peak plasma levels, elimination half-life, and AUC. Exposure (measured by AUC) to valsartan is higher by 70% and the half-life is longer by 35% in the elderly population. Clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderlies.

Renal impairment:
The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. There is no apparent correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. With impaired renal function, the mean elimination half-life of hydrochlorothiazide was doubled in individuals with mild/moderate renal impairment (30 < CrCl < 90 mL/min) and tripled in severe renal impairment (CrCl ≤ 30 mL/min), compared to individuals with normal renal function (CrCl > 90 mL/min).

Hepatic impairment:
Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40% to 60%. On average, patients with mild-to-moderate chronic liver disease have twice the exposure (measured by AUC values) to valsartan.

THERAPEUTIC INDICATIONS

Covam Plus (Amlodipine + Valsartan + Hydrochlorothiazide) is indicated for the treatment of hypertension to lower blood pressure.

DOSAGE & ADMINISTRATION

General Consideration:
The recommended daily dose is once-daily. The dosage may be increased after 2 weeks of therapy. The full blood pressure lowering effect was achieved 2 weeks after being on the maximal dose of Covam Plus (Amlodipine + Valsartan + Hydrochlorothiazide) Tablets. The maximum recommended dose of Covam Plus (Amlodipine + Valsartan + Hydrochlorothiazide) Tablet is 10mg + 320mg + 25mg.

Add-on/Switch Therapy:
Covam Plus (Amlodipine + Valsartan + Hydrochlorothiazide) Tablets may be used for patients not adequately controlled on any 2 of the following antihypertensive classes: calcium channel blockers, angiotensin receptor blockers, and diuretics or in patient who experiences dose-limiting adverse reactions to an individual component while on any dual combination of the components of Covam Plus (Amlodipine + Valsartan + Hydrochlorothiazide) Tablets may be switched to Covam Plus (Amlodipine + Valsartan + Hydrochlorothiazide) Tablets containing a lower dose of that component to achieve similar blood pressure reductions.

Replacement Therapy: Covam Plus (Amlodipine + Valsartan + Hydrochlorothiazide) Tablets may be substituted for the individually titrated components.

Use with Other Antihypertensive Drugs: Covam Plus (Amlodipine + Valsartan + Hydrochlorothiazide) Tablets may be administered with other antihypertensive agents.

Missed Dose: If you miss a dose, take it as soon as you remember. If it is close to your next dose, do not take the missed dose. Just take the next dose at the regular time.

Special Population
Renal Impairment: No dosage adjustment is required for patients with mild to moderate renal impairment. Monitoring of creatinine and potassium levels is advised for patients with moderate renal impairment.

Hepatic Impairment: In patients with mild to moderate hepatic impairment without cholestasis the maximum recommended dose is 80mg valsartan, and therefore, this combination is not suitable in this group of patients.

Heart Failure and Coronary Artery Disease: Caution is advised in patients with heart failure and coronary artery disease, particularly at the maximum dose of Covam Plus (Amlodipine + Valsartan + Hydrochlorothiazide) Tablets is 10mg + 320mg + 25mg.

Elderly (age 65 or above): Caution, including more frequent monitoring of blood pressure, is recommended in elderly patients, particularly at the maximum dose of Covam Plus (Amlodipine + Valsartan + Hydrochlorothiazide) Tablets 10mg + 320mg + 25mg, since available data in this patient population are limited.

ADVERSE REACTIONS

The most common adverse reactions associated with amlodipine, valsartan and hydrochlorothiazide are dizziness, oedema peripheral, headache, dyspepsia, fatigue, muscle spasm, back pain, nausea and nasopharyngitis.

Amlodipine: With amlodipine, gynecomastia has been reported infrequently and a causal relationship is uncertain. Jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis).

Valsartan: The additional adverse reactions reported with use of valsartan or valsartan/hydrochlorothiazide are decrease in hemoglobin, decrease in hematocrit, neutropenia, hypersensitivity, rhabdomyolysis, elevated liver enzymes and reports of hepatitis, impaired renal function, renal failure, alopecia, bullous dermatitis, vasculitis and syncope.

Hydrochlorothiazide: Acute renal failure, renal disorder, aplastic anemia, erythema multiforme, pyrexia, muscle spasm, asthenia, acute angle-closure glaucoma, bone marrow failure, worsening of diabetes control, hypokalemia, blood lipids increased, hyponatremia, hypomagnesemia, hypercalcemia, hyperchloremic alkalosis, impotence, non-melanoma skin cancer and visual impairment.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS

The combination of Amlodipine, Valsartan and Hydrochlorothiazide is contraindicated in:

- Patient with hypersensitivity to the active substances, dihydropyridine derivatives, other sulfonamide-derived drugs, or to any of the excipient of the product.
- Patient with severe hepatic impairment; biliary cirrhosis and cholestasis
- Patient with severe renal impairment (GFR<30ml/min/1.73m^2), anuria and patients undergoing dialysis.
- Patient with refractory hypokalemia, hyponatremia, hypercalcemia and symptomatic hyperuricemia.
- Pregnancy
- Concomitant use with aliskiren in patients with Type 2 diabetes mellitus.
- Children and adolescents (below the age of 18 years).

PRECAUTIONS

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

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. 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 detected, discontinue the use as soon as possible.

Thiazides cross the placenta, and use of thiazides during pregnancy is associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults. Do not initiate treatment with Amlodipine + Valsartan + Hydrochlorothiazide in patients with aortic or mitral stenosis or obstructive hypertrophic cardiomyopathy.

Hypotension in Volume- or Salt-Depleted Patients: In patients with an activated renin-angiotensin system, such as volume or salt depleted patients receiving high doses of diuretics, symptomatic hypotension may occur. Correct this condition prior to administration of the product.

If excessive hypotension occurs with Amlodipine + Valsartan + Hydrochlorothiazide, place the patient in a supine position and, if necessary, give intravenous normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

Increased Angina and/or Myocardial Infarction: Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of amlodipine, particularly in patients with severe obstructive coronary artery disease.

Impaired Renal Function: Changes in renal function, including acute renal failure can be caused by drugs that inhibit the renin-angiotensin system and by diuretics. 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 congestive heart failure, or volume depletion) may be at particular risk of developing acute renal failure. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function.

Potassium Abnormalities: Some patients with heart failure have developed increases in potassium on valsartan. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or valsartan may be required.

Hydrochlorothiazide can cause hypokalemia and hyponatremia. Hypomagnesemia can result in hypokalemia which appears difficult to treat despite potassium repletion. Drugs that inhibit the renin-angiotensin system can cause hyperkalemia. Monitor serum electrolytes periodically. If hypokalemia is accompanied by clinical signs (e.g., muscular weakness, paresis, or ECG alterations), treatment should be discontinued. Correction of hypokalemia and any coexisting hypomagnesemia is recommended prior to the initiation of thiazides.

Hypersensitivity Reaction: 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.

Systemic Lupus Erythematosus: Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Metabolic Imbalances: Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides. Hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricemia and precipitate gout in susceptible patients. Hydrochlorothiazide decreases urinary calcium excretion and may cause elevations of serum calcium. Monitor calcium levels in patients with hypercalcemia.

Acute Myopia and Secondary Angle-Closure Glaucoma: Hydrochlorothiazide can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Angioedema: Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported in patients treated with valsartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors Amlodipine + Valsartan + Hydrochlorothiazide should be immediately discontinued in patients who develop angioedema, and should not be re-administered.

Primary Hyperaldosteronism: Patients with primary hyperaldosteronism will not generally respond to antihypertensive drugs acting through the renin-angiotensin-aldosterone system therefore use of Amlodipine + Valsartan + Hydrochlorothiazide in these patients is not recommended.

Photosensitivity: Cases of photosensitivity reactions have been reported with thiazide diuretics. If photosensitivity reaction occurs during treatment with, Amlodipine + Valsartan + Hydrochlorothiazide, 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.

Hepatic Injury: Cases of clinically significant liver disease have occurred with some angiotensin II receptor antagonists. Hepatitis has been reported rarely with valsartan.

Non-melanoma Skin Cancer: Hydrochlorothiazide is associated with an increased risk of non-melanoma skin cancer. increased risk was predominantly for squamous cell carcinoma (SCC). The risk for non-melanoma skin cancer appears to increase with long-term use. 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 examination of biopsies. The use of hydrochlorothiazide may also need to be reconsidered in patients who have previously experienced non-melanoma skin cancer.

Effects on ability to drive and use machines: When driving vehicles or using machines it should be taken into account that occasionally dizziness or weariness may occur.

Nursing Mothers

It is not known whether valsartan is excreted in human milk. It is reported that amlodipine is excreted in human milk. Hydrochlorothiazide crosses the placenta and is excreted in human milk. It is therefore not advisable for women who are breast-feeding to use this medicine.

DRUG INTERACTIONS

CYP3A Inhibitors: Coadministration with CYP3A inhibitors (moderate and strong) results in increased systemic exposure to amlodipine and may require dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A inhibitors to determine the need for dose adjustment.

CYP3A Inducers: Blood pressure should be closely monitored when amlodipine is co-administered with CYP3A inducers (e.g. rifampicin, St. John's Wort).

Sildenafil: Monitor for hypotension when sildenafil is co-administered with amlodipine.

Simvastatin: Coadministration of simvastatin with amlodipine increases the systemic exposure of simvastatin. Limit the dose of simvastatin in patients on amlodipine to 20mg daily.

Immunosuppressant: Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when co-administered. Frequent monitoring of trough blood levels of cyclosporine and tacrolimus is recommended and adjust the dose when appropriate.

Grapefruit Juice: Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure-lowering effects.

Agents Increasing Serum Potassium: Concomitant use of valsartan with other agents that block the renin-angiotensin system, potassium sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, salt substitutes containing potassium or other drugs that may increase potassium levels (e.g., heparin) may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine. If co-medication is considered necessary, monitoring of serum potassium is advisable.

NSAIDS (COX-2 Inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, coadministration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including valsartan, may result in deterioration of renal function, including possible acute renal failure. The antihypertensive effect of angiotensin II receptor antagonists, including valsartan, may be attenuated by NSAIDs including selective COX-2 inhibitor.

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. Closely monitor blood pressure, renal function and electrolytes in patients on valsartan and other agents that affect the RAS.

Lithium Interaction: Increases in serum lithium concentrations and lithium toxicity have been reported with concomitant use of valsartan or thiazide diuretics. Monitor lithium levels in such patients.

Antidiabetic Drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.

Carbamazepine: May lead to symptomatic hyponatremia.

Ion Exchange Resins: Staggering the dosage of hydrochlorothiazide and ion exchange resins (e.g., cholestyramine, colestipol) such that hydrochlorothiazide is administered at least 4 hours before or 4 to 6 hours after the administration of resins would potentially minimize the interaction.

Cyclosporine: Concomitant treatment with cyclosporine may increase the risk of hyperuricemia and gout-type complications.

Drugs that alter Gastrointestinal Motility: The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g., atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate. Conversely, pro-kinetic drugs may decrease the bioavailability of thiazide diuretics.

Antineoplastic Agents (e.g., cyclophosphamide, methotrexate): Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelo-suppressive effect.

Alcohol, Barbiturates, or Narcotics: Potentiation of orthostatic hypotension may occur.

Skeletal Muscle Relaxants: Possible increased responsiveness to muscle relaxants, such as curare derivatives.

Digitalis Glycosides: Thiazide-induced hypokalemia or hypomagnesemia may predispose the patient to digoxin toxicity.

OVERDOSAGE

The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, institute supportive treatment.

Amlodipine: Over dosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly reflex tachycardia. Experience with intentional overdosage of amlodipine is limited. If massive overdose occurs, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit. Administration of activated charcoal immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption.

Valsartan: Depressed level of consciousness, circulatory collapse, and shock have been reported. Valsartan is not removed from the plasma by hemodialysis.

Hydrochlorothiazide: The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The most common signs and symptoms observed in patients are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis.

STORAGE

Do not store above 30°C.
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the recommended conditions.

HOW SUPPLIED

Covam Plus (Amlodipine + Valsartan + Hydrochlorothiazide) Tablets 5mg+160mg+12.5mg are available in the pack of 28's.
Covam Plus (Amlodipine + Valsartan + Hydrochlorothiazide) Tablets 5mg+160mg+25mg are available in the pack of 28's.
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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.

Manufactured by:
Getz pharma (PVT) LIMITED
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