Covam™

[Amlodipine+Valsartan]

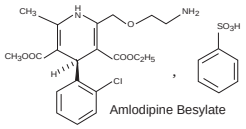
کووام

Tablets

5mg+80mg, 5mg+160mg & 10mg+160mg

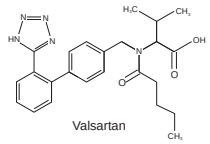
DESCRIPTION

Covam (Amlodipine + Valsartan) is a fixed combination of amlodipine and valsartan. Covam contains the besylate salt of amlodipine, a dihydropyridine calcium-channel blocker. Chemically, Amlodipine besylate is described as 3-Ethyl-5- methyl (4RS)-2-[(2-aminoethoxy) methyl] 4-(2-chlorophenyl)-6-methyl-1, 4-dihydropyridine-3,5-dicarboxylate benzenesulphonate. The molecular formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$ and the structural formula is:



Amlodipine Besylate

Valsartan is a nonpeptide, orally active and specific angiotensin II antagonist acting on the AT_1 receptor subtype. Its chemical name is N-(1-oxopentyl)-N-[[2[1]-(1H-tetrazol-5-yl) [1,1[1]-biphenyl]-4 yl]methyl]-L-valine. The molecular formula is $C_{24}H_{29}N_5O_3$ and the structural formula is:



Valsartan

QUALITATIVE & QUANTITATIVE COMPOSITION

Covam (Amlodipine + Valsartan) is available for oral administration as:

1. Covam Tablets 5mg + 80mg
   Each film-coated tablet contains:
   Amlodipine...5mg
   (as Amlodipine Besylate USP)
   Valsartan USP...80mg

2. Covam Tablets 5mg + 160mg
   Each film-coated tablet contains:
   Amlodipine...5mg
   (as Amlodipine Besylate USP)
   Valsartan USP...160mg

3. Covam Tablets 10mg + 160mg
   Each film-coated tablet contains:
   Amlodipine...10mg
   (as Amlodipine Besylate USP)
   Valsartan USP...160mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Amlodipine and Valsartan are antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension. The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Amlodipine

Amlodipine inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, causing reductions in peripheral vascular resistance and reduction in blood pressure.

Valsartan

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.

Pharmacokinetics

Combination of Amlodipine and Valsartan

Following oral administration of amlodipine and valsartan, peak plasma concentrations of amlodipine and valsartan are reached in 3 and 6 to 8 hours, respectively. The rate and extent of absorption of amlodipine and valsartan are equivalent to the bioavailability of amlodipine and valsartan when administered as individual tablets.

Amlodipine

Absorption

After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6 to12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.

Distribution

Volume of distribution is approximately 21 L/kg. Approximately 97.5% of circulating drug is bound to plasma proteins.

Metabolism

Amlodipine is extensively (approximately 90%) metabolized in the liver to inactive metabolites.

Excretion

Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7 to 8 days. 10% of the parent compound and 60% of amlodipine metabolites are excreted in urine.

Valsartan

Absorption

Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2 to 4 hours. Mean absolute bioavailability is 23%. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%. However, this reduction in AUC is not accompanied by a clinically significant reduction in the therapeutic effect and valsartan can therefore be given with or without food.

Distribution

Valsartan is highly bound to serum proteins (94–97%), mainly serum albumin.

Metabolism

Valsartan is not metabolized to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentration (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive.

Excretion

Valsartan is primarily eliminated in feces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. The half-life of valsartan is 6 hours.

Special population

Elderly

Time to peak plasma amlodipine concentration is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in AUC and elimination half-life.

Renal Impairment

The pharmacokinetics of amlodipine is not significantly influenced by renal insufficiency. 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 insufficiency.

Hepatic Impairment

Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40%-60% in AUC. On average, patients administered with valsartan for the treatment of mild to moderate chronic liver disease, AUC values were found to be doubled.

THERAPEUTIC INDICATIONS

Covam (Amlodipine + Valsartan) is indicated for the treatment of:

- Hypertension.
- Patients whose blood pressure is not adequately controlled on either monotherapy.
- Patients who are likely to need multiple drugs to achieve their blood pressure goals.

DOSAGE AND ADMINISTRATION

The recommended dose of Covam (Amlodipine + Valsartan) is one tablet per day. Covam (Amlodipine + Valsartan) can be used with or without food and it is recommended to take Covam (Amlodipine + Valsartan) with some water.

Covam (Amlodipine + Valsartan) Tablets 5mg + 80mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 5mg or valsartan 80mg alone.

Covam (Amlodipine + Valsartan) Tablets 5mg + 160mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 5mg or valsartan 160mg alone.

Covam (Amlodipine + Valsartan) Tablets 10mg + 160mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 10mg or valsartan 160mg alone or with Covam (Amlodipine + Valsartan) Tablets 5mg + 160mg.

Individual dose titration with the components (i.e. amlodipine and valsartan) is recommended before changing to the fixed dose combination. When clinically appropriate, direct change from monotherapy to the fixed-dose combination may be considered.

The dosage can be increased after 1 to 2 weeks of therapy as needed to control blood pressure. The majority of the antihypertensive effect is attained within 2 weeks after initiation of therapy or a change in dose.

Special Population

Renal impairment

No dosage adjustment is required for patients with mild to moderate renal impairment. Monitoring of potassium levels and creatinine is advised in moderate renal impairment.

Hepatic impairment

Caution should be exercised when administering Covam (Amlodipine + Valsartan) to patients with hepatic impairment or biliary obstructive disorders. In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80mg valsartan. Amlodipine dosage recommendations have not been established in patients with mild to moderate hepatic impairment. When switching eligible hypertensive patients with hepatic impairment to amlodipine or Covam (Amlodipine + Valsartan), the lowest available dose of amlodipine monotherapy or of the amlodipine component, respectively, should be used.

Elderly (age 65 years or over)

In elderly patients, caution is required when increasing the dosage. When switching eligible elderly hypertensive patients to amlodipine or Covam (Amlodipine + Valsartan), the lowest available dose of amlodipine monotherapy or of the amlodipine component, respectively, should be used.

Pediatric population

The safety and efficacy of Covam (Amlodipine + Valsartan) in children aged below 18 years have not been established.

ADVERSE REACTIONS

Common:

Nasopharyngitis, influenza, hypokalemia, headache, asthenia, fatigue, facial edema, flushing, hot flush, edema, edema peripheral and pitting edema.

210mm

135mm

Uncommon:
Anorexia, hypercalcemia, hyperlipidemia, hyperuricemia, hyponatremia, coordination abnormal, dizziness, dizziness postural, paraesthesia, somnolence, visual impairment, vertigo, palpitations, tachycardia, orthostatic hypotension, cough, pharyngolaryngeal pain, abdominal discomfort, abdominal pain upper, constipation, diarrhea, dry mouth, nausea, erythema, rash, arthralgia, back pain and joint swelling.

Rare:
Hypersensitivity, anxiety, visual disturbance, tinnitus, syncope, hypotension, exanthema, hyperhidrosis, pruritus, muscle spasm, sensation of heaviness, pollakiuria, polyuria and erectile dysfunction.

CONTRAINDICATIONS
The combination of amlodipine and valsartan is contraindicated in:
- Patients with known hypersensitivity to the active substances, to dihydropyridine derivatives or to any of the excipient of the product.
- Severe hepatic impairment, biliary cirrhosis or cholestasis.
- Patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) using concomitantly aliskiren-containing products.
- Second and third trimesters of pregnancy.
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g. hypertrophic obstructive cardiomyopathy and high grade aortic stenosis).
- Hemodynamically unstable heart failure after acute myocardial infarction.

Nursing Mothers
The combination of amlodipine and valsartan is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

PRECAUTIONS
Hypertensive crisis
The safety and efficacy of amlodipine in hypertensive crisis have not been established.

Pregnancy
Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

Sodium- and/or volume-depleted patients
In patients with an activated renin-angiotensin system (such as volume and/or salt depleted patients receiving high doses of diuretics) who are receiving angiotensin receptor blockers, symptomatic hypotension may occur. Correction of this condition prior to administration of combination of amlodipine + valsartan or close medical supervision at the start of treatment is recommended.

Hyperkalemia
Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (heparin, etc.) should be undertaken with caution and with frequent monitoring of potassium levels.

Renal artery stenosis
Combination of amlodipine + valsartan should be used with caution to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis to a solitary kidney since blood urea and serum creatinine may increase in such patients.

Hepatic impairment
Particular caution should be exercised when administering combination of amlodipine + valsartan to patients with mild to moderate hepatic impairment or biliary obstructive disorders. In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80mg valsartan.

Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with the angiotensin II antagonist valsartan as their renin-angiotensin system is affected by the primary disease.

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. Combination of amlodipine + valsartan should be discontinued immediately in patients who develop angioedema and should not be re-administered.

Heart failure/post-myocardial infarction
Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function. Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Aortic and mitral valve stenosis
As with all other vasodilators, special caution is indicated in patients suffering from mitral stenosis or significant aortic stenosis that is not high grade.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
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 ARBs should not be used concomitantly in patients with diabetic nephropathy.

DRUG INTERACTIONS
Other antihypertensive agents
Commonly used antihypertensive agents and other medicinal products which may cause hypotensive adverse effects may increase the antihypertensive effect of the combination.

Grapefruit or 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.

CYP3A4 inhibitors
Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers
The concomitant use of CYP3A4 inducers (e.g. rifampicin, Hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

Simvastatin
Co-administration of multiple doses of 10mg amlodipine with 80mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. It is recommended to limit the dose of simvastatin to 20mg daily in patients on amlodipine.

Dantrolene (infusion)
Due to risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists, including valsartan. Therefore, careful monitoring of serum lithium levels is recommended during concomitant use. If a diurectic is also used, the risk of lithium toxicity may presumably be increased further with combination of amlodipine and valsartan.

Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels
If a medicinal product that affects potassium levels is to be prescribed in combination with valsartan, monitoring of potassium plasma levels is advised.

Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid (>3 g/day), and non-selective NSAIDs
When angiotensin II antagonists are administered simultaneously with NSAIDs attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

Inhibitors of the uptake transporter (rifampicin, cyclosporine) or efflux transporter (ritonavir)
The results of an in vitro study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and of the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (rifampicin, cyclosporine) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.

Dual blockade of the RAAS with ARBs, ACE inhibitors or aliskiren
Dual blockade of the RAAS through the combined use of ACE inhibitors, ARBs or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.

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

Immunosuppressants
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.

OVERDOSAGE
Symptoms
The major symptom of overdose with valsartan is possibly pronounced hypotension with dizziness. Overdose with amlodipine may result in excessive peripheral vasodilation and, possibly, reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome may occur.

Treatment
If ingestion is recent, induction of vomiting or gastric lavage may be considered. Administration of activated charcoal immediately or up to two hours after ingestion of amlodipine can significantly decrease amlodipine absorption. Clinically significant hypotension due to the combination of amlodipine and valsartan overdose calls for active cardiovascular support, including frequent monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Both valsartan and amlodipine are unlikely to be removed by hemodialysis.

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

HOW SUPPLIED
Covam (Amlodipine + Valsartan) Tablets 5mg + 80mg are available in pack of 14's.
Covam (Amlodipine + Valsartan) Tablets 5mg + 160mg are available in pack of 14's.
Covam (Amlodipine + Valsartan) Tablets 10mg + 160mg are available in pack of 14'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.

Manufactured by:
Getz pharma (PVT) LIMITED
www.getzpharma.com
29-30/27, K.I.A., Karachi, Pakistan
L-200008921

210mm

135mm