caloc-V® Tablets

(Amlodipine+Valsartan)

کیلوک-وی ٹیبلیٹس

(ایملوڈِپین + ویلسارٹن)

WARNING: AVOID USE IN PREGNANCY
When pregnancy is detected, discontinue as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus.

QUALITATIVE AND QUANTITATIVE COMPOSITION
Caloc-V Tablets 5mg+80mg
Each film-coated tablet contains:
Amlodipine…5mg as Amlodipine Besylate USP
Valsartan USP ……80mg
(Product Specs: USP)

Caloc-V Tablets 10mg+160mg
Each film-coated tablet contains:
Amlodipine…10mg as Amlodipine Besylate USP
Valsartan USP…160mg
(Product Specs: USP)

Caloc-V Tablets 5mg+160mg
Each film-coated tablet contains:
Amlodipine ….5mg as Amlodipine Besylate USP
Valsartan USP…160mg
(Product Specs: USP)

PHARMACEUTICAL FORM
Film coated Tablets

CLINICAL PARTICULARS
Therapeutic Indications
Treatment of essential hypertension. Caloc-V is indicated in
- Adults whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy.
- As initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals

Posology and method of administration
Posology
The recommended dose of Caloc-V is one tablet per day.
Caloc-V 10 mg+160 mg film-coated tablets may be administered in patients whose blood pressure is not adequately controlled with amlodipine 10 mg or valsartan 160 mg alone or with Amlodipine + Valsartan 5 mg+160 mg. When clinically appropriate, direct change from monotherapy to the fixed-dose combination may be considered.
For convenience, patients receiving valsartan and amlodipine from separate tablets may be switched to Caloc-V containing the same component doses.

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
Amlodipine + Valsartan is contraindicated in patients with severe hepatic impairment. Caution should be exercised when administering 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 80 mg 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 + Valsartan, the lowest available dose of amlodipine monotherapy or of the amlodipine component, respectively, should be used.

Elderly (age ≥ 65 years)
In elderly patients, caution is required when increasing the dosage. When switching eligible elderly hypertensive patients to amlodipine or Amlodipine + Valsartan, the lowest available dose of amlodipine monotherapy or of the amlodipine component, respectively, should be used.

Paediatric population: No data are available.

Method of administration
Oral use. It is recommended to take with some water. Caloc-V tablets can be used with or without food.

Contraindications
- Hypersensitivity to the active substances, to dihydropyridine derivatives
- Severe hepatic impairment, biliary cirrhosis or cholestasis.
- Concomitant use with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m2)
- 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).
- Haemodynamically unstable heart failure after acute myocardial infarction.

Special warnings and precautions for use
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.

Sodium-and/or volume-depleted patients: If hypotension occurs with Amlodipine + Valsartan, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. Treatment can be continued once blood pressure has been stabilised. Close medical supervision at the start of treatment is recommended.

Hyperkalaemia: 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: 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.

Kidney transplantation: There is no experience of the safe use of Amlodipine + Valsartan in patients who have had a recent kidney transplantation.

Hepatic impairment: Valsartan is mostly eliminated unchanged via the bile. The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Particular caution should be exercised when administering 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 80 mg valsartan.

Renal impairment: No dosage adjustment of Amlodipine + Valsartan is required for patients with mild to moderate renal impairment (GFR > 30 mL/min/1.73 m^2). Monitoring of potassium levels and creatinine is advised in moderate renal impairment.

Primary hyperaldosteronism: Patients with primary hyperaldosteronism should not be treated with the AIIRA 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. Amlodipine + Valsartan should be discontinued immediately in patients who develop angioedema and should not be re-administered.
Heart failure / post-myocardial infarction: In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with valsartan.
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: 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): Dual blockade of RAAS through the combined use of ACE inhibitors, ARBs or aliskiren is therefore not recommended. 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.

Interaction with other medicinal products and other forms of interaction
Interactions common to the combination: No drug-drug interaction studies have been performed with Amlodipine + Valsartan and other medicinal products.

To be taken into account with concomitant use of Other antihypertensive agents
Commonly used antihypertensive agents (e.g. α-blockers, diuretics) and other medicinal products which may cause hypotensive adverse effects (e.g. tricyclic antidepressants, α-blockers for treatment of benign prostate hyperplasia) may increase the antihypertensive effect of the combination.

Interactions linked to amlodipine;
Concomitant use not recommended:
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.

Caution required with concomitant use
CYP3A4 inhibitors: Concomitant use of amlodipine with azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure resulting in an increased risk of hypotension. Close clinical observation of patients is recommended and dose adjustment may thus be required.
Blood pressure should be monitored in CYP3A4 inducers (anticonvulsant agents e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone, rifampicin, Hypericum perforatum) and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum).

Tacrolimus: There is a risk of increased tacrolimus blood levels when co-administered with amlodipine. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring and dose adjustment of tacrolimus when appropriate.

Simvastatin: It is recommended to limit the dose of simvastatin to 20 mg daily in patients on amlodipine.

Dantrolene (infusion): Due to risk of hyperkalaemia, 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.

To be taken into account with concomitant use
Others: Amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or ciclosporin.

Interactions linked to valsartan: Concomitant use not recommended
Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors or AIIRAs, including valsartan. Therefore, careful monitoring of serum lithium levels is recommended during concomitant use. If a diuretic is also used, the risk of lithium toxicity may presumably be increased further with Amlodipine + 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.

Caution required with concomitant use: Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid (>3 g/day), and non-selective NSAIDs.
Concomitant use of AIIRAs 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, ciclosporin) or efflux transporter (ritonavir)
Co-administration of inhibitors of the uptake transporter (rifampicin, ciclosporin) 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, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent

Others: In monotherapy with valsartan, no interactions of clinical significance have been found with the following substances: Cimetidine, Warfarin, Furosemide, Digoxin, Atenolol, Indometacin, Hydrochlorothiazide, Amlodipine, Glibenclamide.

Fertility, Pregnancy and Lactation
Pregnancy
Amlodipine: Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and fetus.

Valsartan: The use of AIIRAs is not recommended during the first trimester of pregnancy The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy.

Breast-feeding (Lactation)
Amlodipine
Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3-7%, with a maximum of 15%. The effect of amlodipine on infants is unknown.

Amlodipine + Valsartan
Amlodipine+valsartan is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a new-born or preterm infant.

Effects on ability to drive and use machines
Patients taking Amlodipine + Valsartan and driving vehicles or using machines should take into account that dizziness or weariness may occasionally occur. Amlodipine can have mild or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired.

Undesirable effects
Adverse reactions have been ranked under headings of frequency 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); not known (cannot be estimated from the available data).

Common: Nasopharyngitis & influenza, Hypokalaemia, Headache, Asthenia, Fatigue, Facial edema, Flushing, Hot flush, Edema, Oedema Peripheral, Pitting edema

Uncommon: Anorexia, Hypercalcaemia, Hyperlipidaemia, Hyperuricaemia, Hyponatraemia, Coordination abnormal, Dizziness, Dizziness postural, Paraesthesia, Hypoesthesia, Somnolence, Visual Impairment, Vertigo, Palpitations, Tachycardia, Cough, Dyspnea, Pharyngo laryngeal pain, Abdominal discomfort, Abdominal pain upper, Constipation, Diarrhoea, Dry mouth, Dyspepsia, Nausea, Vomiting, Erythema, Erythema multiforme, Rash, Arthralgia, Back pain, Joint swelling

Rare: Hypersensitivity, Depression, Anxiety, Visual disturbance, Tinnitus, Syncope, Hypotension, Orthostatic hypotension, Pruritus, Purpura, Exanthema, Hyperhidrosis, Muscle spasm, Sensation of heaviness, Nocturia, Pollakuria, Polyuria, Erectile dysfunction.

Overdose
If massive overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. Hemodialysis is not likely to be of benefit.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: agents acting on the renin-angiotensin system, angiotensin II receptor blockers (ARBs) and calcium channel blockers, ATC code: C09DB01.

Mechanism of action:
Amlodipine + Valsartan combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: amlodipine belongs to the calcium antagonist class and valsartan to the angiotensin II antagonist class of medicines. The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Amlodipine+valsartan
The combination of Amlodipine+valsartan produces dose-related additive reduction in blood pressure across its therapeutic dose range. The antihypertensive effect of a single dose of the combination persisted for 24 hours.

Amlodipine: The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, causing reductions in peripheral vascular resistance and in blood pressure.

Plasma concentrations correlate with effect in both young and elderly patients.
In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow, without change in filtration fraction or proteinuria. Amlodipine does not change Sino atrial nodal function or atrioventricular conduction in intact animals or humans.

Valsartan
Valsartan is an orally active, potent and specific angiotensin II receptor antagonist. It acts selectively on the receptor subtype AT1, which is responsible for the known actions of angiotensin II. Valsartan does not exhibit any partial agonist activity at the AT1 receptor and has much (about 20,000-fold) greater affinity for the AT1 receptor than for the AT2 receptor. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing.
Administration of valsartan to patients with hypertension results in a drop in blood pressure without affecting pulse rate.

Pharmacokinetic properties
Linearity: Amlodipine+valsartan exhibit linear pharmacokinetics.

Amlodipine+valsartan
Following oral administration of Amlodipine + Valsartan, peak plasma concentrations of valsartan and amlodipine are reached in 3 and 6 – 8 hours, respectively. The rate and extent of absorption of Amlodipine + Valsartan are equivalent to the bioavailability of valsartan and amlodipine 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 – 12 hours. Absolute bioavailability has been calculated as between 64 – 80%. Amlodipine bioavailability is unaffected by food ingestion.

Distribution: Volume of distribution is approximately 21L/kg. In vitro studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins.

Biotransformation: Amlodipine is extensively (approximately 90%) metabolised in the liver to inactive metabolites.

Elimination: Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 – 50 hours. Steady-state plasma levels are reached after continuous administration for 7 – 8 days. 10% of original amlodipine 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 – 4 hours. Mean absolute bioavailability is 23%. Valsartan can therefore be given either with or without food.

Distribution: The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres, indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94 – 97%), mainly serum albumin.

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

Elimination: Valsartan shows multi-exponential decay kinetics (t½α < 1 hour and t½ß about 9 hours). Valsartan is primarily eliminated in faeces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2L/h and its renal clearance is 0.62L/h (about

30% of total clearance). The half-life of valsartan is 6 hours.

Special populations
Paediatric population (age below 18 years): No pharmacokinetic data are available in the paediatric population.

Elderly (age ≥ 65 years): Time to peak plasma amlodipine concentrations is similar in young and elderly patients. Mean systemic AUC of valsartan is higher by 70% in the elderly than in the young, therefore caution is required when increasing the dosage.

Renal impairment: The pharmacokinetics of amlodipine are not significantly influenced by renal impairment.

Hepatic impairment: Patients with hepatic impairment have decreased clearance of amlodipine with resulting increase of approximately 40 – 60% in AUC.

PHARMACEUTICAL PROPERTIES
Incompatibilities
Not Applicable.

Shelf life
2 Years

Special Precautions and Storage:
Protect from heat, sunlight & moisture, store below 30°C.
The expiration date refers to the product correctly stored at the required condition.
Keep out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:
Caloc-V Tablets 5 mg+80 mg: Cold form & Cold seal Alu Alu Pack of 14 tablets
Caloc-V Tablets 10 mg+160 mg: Cold form & Cold seal Alu Alu Pack of 14 tablets
Caloc-V Tablets 5 mg+160 mg: Cold form & Cold seal Alu Alu Pack of 14 tablets

REGISTRATION HOLDER
MARKETING AUTHORIZATION HOLDER
Head Office:
Bosch Pharmaceuticals (Pvt.) Ltd.,
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MANUFACTURER
Bosch Pharmaceuticals (Pvt.) Ltd.,
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REGISTRATION / MARKETING AUTHORIZATION NUMBER
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Caloc-V Tablets 10 mg+160 mg: 088909
Caloc-V Tablets 5 mg+160 mg: 088910

DATE FROM WHICH MARKETING IS AUTHORIZED/RENEWAL OF THE AUTHORIZATION
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ہدایات:۔
دھوپ، گرمی اور نمی سے محفوظ ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
بچوں کی پہنچ سے دُور رکھیں۔
صرف مستند ڈاکٹر کے نسخے پر فروخت کے لئے۔

Manufactured by:
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Karachi - Pakistan