Exval®-A

(Amlodipine / Valsartan)
Tablets U.S.P.

5mg /80mg
5mg /160mg
10mg /160mg

ایکسویل-اے
(ایملوڈیپائین/ولسارٹن)
ٹیبلٹس یو-ایس-پی-

۵ملی گرام / ۸۰ملی گرام
۵ملی گرام / ۱۶۰ملی گرام
۱۰ملی گرام / ۱۶۰ملی گرام ٹیبلٹس

QUALITATIVE AND QUANTITATIVE COMPOSITION

Exval®-A 5mg / 80mg Tablets

Each film-coated tablet contains:
Amlodipine Besilate B.P. eq. to Amlodipine......5mg
Valsartan U.S.P. 80mg

Exval®-A 5mg / 160mg Tablets

Each film-coated tablet contains:
Amlodipine Besilate B.P. eq. to Amlodipine.......5mg
Valsartan U.S.P. 160mg

Exval®-A 10mg / 160mg Tablets

Each film-coated tablet contains:
Amlodipine Besilate B.P. eq. to Amlodipine......10mg
Valsartan U.S.P. 160mg

WARNING: FETAL TOXICITY
- When pregnancy is detected, discontinue Exval®-A as soon as possible.
- Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

DESCRIPTION

Exval-A is a fixed combination of amlodipine and valsartan. Exval-A contains the Besilate salt of amlodipine, a dihydropyridine calcium-channel blocker (CCB) and Valsartan is a nonpeptide, orally active, and specific angiotensin II antagonist acting on the AT1 receptor subtype.

CLINICAL PHARMACOLOGY

Mechanism of Action: Amlodipine: Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. **Valsartan:** Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland.

Pharmacodynamics: Amlodipine: Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures.

Valsartan: Valsartan inhibits the pressor effect of angiotensin II infusions. Administration of valsartan to patients with essential hypertension results in a significant reduction of sitting, supine, and standing systolic blood pressure, usually with little or no orthostatic change.

Exval-A: Exval®-A has been shown to be effective in lowering blood pressure. Both amlodipine and valsartan lower blood pressure by reducing peripheral resistance, but calcium influx blockade and reduction of angiotensin II vasoconstriction are complementary mechanisms.

Pharmacokinetics: Amlodipine: Peak plasma concentrations of amlodipine are reached 6 to 12 hours after administration of amlodipine alone. Absolute bioavailability is 64% and 90% and is not altered by the presence of food. The apparent volume of distribution of amlodipine is 21 L/kg. 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%). Food decreases the exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (Cmax) by about 50%. 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.

Exval®-A: Following oral administration of Exval®-A in normal healthy adults, peak plasma concentrations of valsartan and amlodipine are reached in 3 and 6 to 8 hours, respectively. The rate and extent of absorption of valsartan and amlodipine from Exval®-A are the same as when administered as individual tablets. The bioavailabilities of amlodipine and valsartan are not altered by the coadministration of food.

INDICATIONS AND USAGE

Exval-A is indicated for the treatment of hypertension, to lower blood pressure:
- In patients not adequately controlled on monotherapy.
- As initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals.

Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.

CONTRAINDICATIONS

- Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients.
- Concomitant use of Exval-A with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2).
- Severe hepatic impairment, biliary cirrhosis or cholestasis.
- 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.

INTERACTIONS

Other antihypertensive agents: Commonly used antihypertensive agents may increase the antihypertensive effect of the combination.

Amlodipine: 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 may give rise to significant increase in amlodipine exposure. **CYP3A4 inducers (anticonvulsant agents[e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, Hypericum perforatum):** Amlodipine should be used with caution together with CYP3A4 inducers. **Simvastatin:** It is recommended to limit the dose of simvastatin to 20mg daily in patients on amlodipine.

Sildenafil: Monitor for hypotension when sildenafil is co-administered with amlodipine. **Dantrolene (infusion):** In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. **Immunosuppressants:** Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when co-administered.

- **Valsartan: Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors):** Monitor renal function periodically in patients receiving valsartan and NSAID therapy. **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. **Transporters:** Coadministration of inhibitors of the uptake transporter (rifampin, cyclosporine) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan. **Dual blockade of the RAAS with ARBs, ACE inhibitors or aliskiren:** Clinical trial data have shown that 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.

Lithium: Monitor serum lithium levels during concomitant use.

USE IN SPECIFIC POPULATION

Pregnancy: Category D: Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death are associated with it. It is contraindicated in all trimesters of pregnancy.

Labor and Delivery: The effect of Exval-A on labor and delivery has not been studied.

Nursing mothers: It is not known whether amlodipine or valsartan is excreted in human milk.

Pediatric Use: Safety and effectiveness of Exval-A in pediatric patients have not been established. **Neonates with a history of in utero exposure to Exval®-A:** If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. **Geriatric Use:** Greater sensitivity of some older individuals cannot be ruled out.

PRECAUTIONS

Fetal Toxicity: Pregnancy Category D: When pregnancy is detected, discontinue Exval-A as soon as possible.

Hypotension: Excessive hypotension was seen in patients with uncomplicated hypertension. Initiate therapy cautiously in patients with heart failure or recent myocardial infarction and in patients undergoing surgery or dialysis.

Risk of Myocardial Infarction or Increased Angina: 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:** Monitor renal function periodically in these patients.

Hyperkalemia: Drugs that inhibit the renin-angiotensin system can cause hyperkalemia. Monitor serum electrolytes periodically. Dosage reduction and/or discontinuation of Exval-A may be required. **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 Exval-A 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 Exval-A is required for patients with mild to moderate renal impairment (GFR >30 ml/min/1.73 m2). Monitoring of potassium levels and creatinine is advised in moderate renal impairment. **Primary hyperaldosteronism:** Patients with primary hyperaldosteronism should not be treated with valsartan. **Angioedema:** Exval-A should be discontinued immediately in patients who develop angioedema and should not be re-administered.

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): Dual blockade of RAAS through the combined use of ACE inhibitors, ARBs or aliskiren not recommended. ACE inhibitors and ARBs should not be used concomitantly in patients with diabetic nephropathy. **Effects on ability to drive and use machines:** If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired so avoid to drive and use machine.

ADVERSE REACTIONS

Lymphadenopathy, tachycardia, abdominal discomfort, dry mouth, colitis, fatigue, chest pain, asthenia, pitting edema, sinusitis, bronchitis, pharyngitis, gastroenteritis, pharyngotonsillitis, bronchitis acute, epicondylitis, limb injury, gout, non-insulin-dependent diabetes mellitus, hypercholesterolemia, arthralgia, muscle spasms, myalgia, osteoarthritis, musculoskeletal chest pain ,headache, sciatica, paresthesia, cervicobrachial syndrome, carpal tunnel syndrome, hematuria, nephrolithiasis, erectile dysfunction, dyspnea, epistaxis, productive cough, pruritus, rash, hyperhidrosis, eczema, erythema flushing.

Side effects: •Swelling (edema) of the hands, ankles, or feet •nasal congestion, sore throat, and discomfort when swallowing •upper respiratory tract infection (head or chest cold) •dizziness.

DOSAGE AND ADMINISTRATION

The recommended administration of Exval®-A is one tablet per day. It is recommended to take Exval®-A with some water. The dosage can be increased after 1 to 2 weeks of therapy to a maximum of one 10/320 mg tablet once daily 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. Exval-A may be administered with or without food. Exval®-A may be administered with other antihypertensive agents.

Add-on Therapy: A patient whose blood pressure is not adequately controlled with amlodipine (or another dihydropyridine calcium-channel blocker) alone or with valsartan (or another angiotensin II receptor blocker) alone may be switched to combination therapy with Exval®-A.

Replacement Therapy: For convenience, patients receiving amlodipine and valsartan from separate tablets may instead wish to receive tablets of Exval®-A containing the same component doses.

Initial Therapy: A patient may be initiated on Exval®-A if it is unlikely that control of blood pressure would be achieved with a single agent. The usual starting dose is **Exval®-A 5mg/160mg** once daily in patients who are not volume-depleted. **Exval®-A 5mg/80mg** may be administered in patients whose blood pressure is not adequately controlled with amlodipine 5mg or valsartan 80mg alone. **Exval®-A 5mg/160mg** may be administered in patients whose blood pressure is not adequately controlled with amlodipine 5mg or valsartan 160mg alone. **Exval®-A 10mg/160mg** may be administered in patients whose blood pressure is not adequately controlled with amlodipine 10mg or valsartan 160mg alone or with Exval®-A 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.

Renal impairment: There are no available clinical data in severely renally impaired patients. 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: Exval®-A is contraindicated in patients with severe hepatic impairment. Caution should be exercised when administering Exval®-A 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 or Exval®-A, 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.

Paediatric population: The safety and efficacy of Exval®-A in children aged below 18 years have not been established.

Overdosage: There is no experience of overdose with Exval-A. 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 have been reported.

Treatment: If ingestion is recent, induction of vomiting or gastric lavage may be considered. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption. Clinically significant hypotension due to Exval®-A 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.

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 your regular time.

INSTRUCTIONS

Dosage as directed by the physician.
Store at 25°C, excursions permitted to 15°C - 30°C.
Protect from sunlight and moisture.
Keep all medicines out of the reach of children.

PRESENTATION

Exval®-A 5mg / 80mg (Amlodipine 5mg / Valsartan 80mg) tablets are available in Alu-Alu blister pack of 14's.
Exval®-A 5mg / 160mg (Amlodipine 5mg / Valsartan 160mg) tablets are available in Alu-Alu blister pack of 14's.
Exval®-A 10mg / 160mg (Amlodipine 10mg / Valsartan 160mg tablets are available in Alu-Alu blister pack of 14's.

علامات/طریقہ استعمال:

ایکسوویل۔اے اُن مریضوں کے لئے تجویز کردہ ہے جس میں ہائی بلڈ پریشر
مونوتھراپی سے کنٹرول نہ ہو سکے۔
عمومی خوراک ایک ٹیبلٹ روزانہ ہے۔
ایکسوویل۔اے ٹیبلٹ کھانے کے ساتھ یا بغیر کھانے کے لی جا سکتی ہے۔
تھراپی کے اسے ۲ ہفتے بعد خوراک ڈاکٹر کی ہدایت کے مطابق بڑھائی جا سکتی ہے
جو کہ 10/320 ملی گرام یومیہ ہے۔

مضر اثرات:

ہاتھوں، ٹخنوں اور پاؤں میں سوجن، پھیپھڑوں کا انفکشن، بند ناک،
گلے میں تکلیف اور چکر۔

احتیاطی تدابیر:

حاملہ خواتین ہرگز استعمال نہ کریں۔
میٹوکارڈیئل انفارکشن اور انجائنا ہونے کا خطرہ موجود ہے۔
جگر اور گردے کے مریض احتیاط سے استعمال کریں۔

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
۲۵ ڈگری سینٹی گریڈ پر رکھیں، محفوظ رکھنے کی حد ۱۵ سے ۳۰ ڈگری سینٹی گریڈ ہے۔
سورج کی روشنی اور نمی سے محفوظ رکھیں۔تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

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