Exval®-AH

(Amlodipine/Valsartan/Hydrochlorothiazide)

5mg/160mg/12.5mg
5mg/160mg/25mg
10mg/160mg/12.5mg
10mg/160mg/25mg
10mg/320mg/25mg
Tablets

ایکسویل۔اے ایچ

(ایملوڈیپائین/ولسارٹن/ہائڈروکلوروتھیازائڈ)
ٹیبلٹس یو۔ایس۔پی۔

QUALITATIVE AND QUANTITATIVE COMPOSITION

Exval®-AH Tablet U.S.P. 5mg/160mg/12.5mg: Each film-coated tablet contains:
Amlodipine Besilate B.P. eq. to Amlodipine..... 5mg
Valsartan U.S.P. ……160mg
Hydrochlorothiazide B.P. 12.5mg
Exval®-AH Tablet U.S.P. 5mg/160mg/25mg: Each film-coated tablet contains:
Amlodipine Besilate B.P. eq. to Amlodipine.....5mg
Valsartan U.S.P. ……160mg
Hydrochlorothiazide B.P. 25mg
Exval®-AH Tablet U.S.P 10mg/160mg/12.5mg: Each film-coated tablet contains:
Amlodipine Besilate B.P. eq. to Amlodipine.....10mg
Valsartan U.S.P. ……160mg
Hydrochlorothiazide B.P. 12.5mg
Exval®-AH Tablet U.S.P. 10mg/160mg/25mg: Each film-coated tablet contains:
Amlodipine Besilate B.P. eq. to Amlodipine.....10mg
Valsartan U.S.P. ……160mg
Hydrochlorothiazide B.P. 25mg
Exval®-AH Tablet U.S.P. 10mg/320mg/25mg: Each film-coated tablet contains:
Amlodipine Besilate B.P. eq. to Amlodipine.....10mg
Valsartan U.S.P. ……320mg
Hydrochlorothiazide B.P. 25mg

WARNING: FETAL TOXICITY

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

DESCRIPTION: Exval-AH tablet is a fixed combination of amlodipine, valsartan and hydrochlorothiazide. Exval-AH tablet contains the (besylate salt of amlodipine) a dihydropyridine calcium channel blocker (CCB), (Valsartan) a nonpeptide, orally active, and specific angiotensin II antagonist acting on the AT1 receptor subtype and (Hydrochlorothiazide) a thiazide diuretic.

CLINICAL PHARMACOLOGY: Mechanism of Action: Amlodipine blocks the contractile effects of calcium on cardiac and vascular smooth muscle cells; Valsartan blocks the vasoconstriction and sodium retaining effects of angiotensin II on cardiac, vascular smooth muscle, adrenal and renal cells; and Hydrochlorothiazide directly promotes the excretion of sodium and chloride in the kidney leading to reductions in intravascular volume. **Pharmacodynamics:** Amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. Valsartan inhibits the pressor effect of angiotensin II infusions. Hydrochlorothiazide, diuresis begins within 2 hours after oral administration, peaks in about 4 hours and lasts about 6 to 12 hours. **Pharmacokinetics:** Amlodipine: Peak plasma concentrations of amlodipine are reached 6-12 hours after administration of amlodipine alone. Elimination of amlodipine from the plasma is biphasic with a terminal elimination half-life of about 30-50 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. **Hydrochlorothiazide:** Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated as unchanged drug within 24 hours. The elimination half-life is between 5.8 and 18.9 hours. **Renal insufficiency: Valsartan:** Dose adjustment is not required in patients with mild to moderate renal dysfunction. In case of severe renal disease, exercise care with dosing of Valsartan. Hydrochlorothiazide: The half-life of hydrochlorothiazide elimination lengthens to 21 hours in patients with impaired renal functions (mean creatinine clearance of 19mL/min). **Hepatic Insufficiency: Amlodipine:** Patients with hepatic insufficiency have de-

creased clearance of amlodipine with resulting increase in AUC of approximately 40%-60%; therefore, a lower initial dose of amlodipine may be required. Valsartan: Care should be exercised in patients with liver disease.

INDICATION: Treatment of essential hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of amlodipine, valsartan and hydrochlorothiazide (HCT), taken either as three single-component formulations or as a dual-component and a single-component formulation.

CONTRAINDICATIONS: Hypersensitivity to the active substances, to other sulphonamide derivatives to dihydropyridine Derivatives or to any of the excipients, second and third trimesters of pregnancy, hepatic impairment, biliary cirrhosis or cholestasis, severe renal impairment (GFR <30 ml/min/1.73 m2), anuria and patients undergoing dialysis, concomitant use of Exval-AH with aliskiren-containing products in patients with diabetes mellitus, refractory hypokalaemia, hyponatraemia, hypercalcaemia, symptomatic hyperuricaemia, 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.

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. **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:** Transporters: Coadministration of inhibitors of the uptake transporter (rifampin, cyclosporine) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan. **Lithium:** Monitor serum lithium levels during concomitant use. **Hydrochlorothiazide:** Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension may occur. **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 use with cyclosporine may increase the risk of hyperuricemia and gouttype complications. **Skeletal muscle relaxants:** Possible increased responsiveness to muscle relaxants such as curare derivatives. **Drugs that alter gastrointestinal motility:** The bioavailability of thiazidetype diuretics may be increased by anti-cholinergic agents (e.g., atropine, biperiden). Cholestyramine and colestipol: Reduced absorption of thiazides occur when these drugs are taken before hydrochlorothiazide. **Antineoplastic agents (e.g., cyclophosphamide, methotrexate):** Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects. **Digitalis glycosides:** Thiazide-induced hypokalemia or hypomagnesemia may predispose the patient to digoxin toxicity. **Caution with digoxin or other digitalis glycosides (medicines used to treat heart problems)Corticosteroids, ACTH:** Intensified electrolyte depletion, particularly hypokalemia. **Lithium:** Should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Non-steroidal anti-inflammatory drugs: In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. **USE IN SPECIFIC POPULATION: Pregnancy Category D:** Avoid use in pregnancy. Exval-AH can cause harm to the fetus when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. **Nursing Mothers:** Avoid use while nursing – discontinue either nursing or drug. **Geriatric Patients:** No overall differences in the efficacy or safety of Exval-AH was observed in this patient population, but greater sensitivity of some older individuals cannot be

ruled out. **Pediatric Use:** The safety and effectiveness of Exval-AH in pediatric patients have not been established.

WARNINGS AND PRECAUTIONS: Hypotension in Volume- or Salt-Depleted Patients: Symptomatic hypotension may occur in patients receiving angiotensin receptor blockers. Correct this condition prior to administration of Exval-AH. Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration. Do not initiate treatment with Exval-AH in patients with aortic or mitral stenosis or obstructive hypertrophic cardiomyopathy. **Increased Angina and/or Myocardial Infarction:** Patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration or severity of angina or acute myocardial infarction upon starting calcium channel blocker therapy or at the time of dosage increase. **Impaired Hepatic Function:** As the majority of valsartan is eliminated in the bile, patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders, showed lower valsartan clearance (higher AUCs). In patients with impaired hepatic function or progressive liver disease, minor alterations of fluid and electrolyte balance, such as those resulting from diuretic use, may precipitate hepatic coma. Avoid the use of Exval-AH in patients with severe hepatic impairment. **Impaired Renal Function:** In patients with severe heart failure, treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with valsartan. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function. Avoid use of Exval-AH in severe renal disease (creatinine clearance ≤30 mL/min). The usual regimens of therapy with Exval-AH may be followed if the patient's creatinine clearance is >30 mL/min. **Heart Failure: Amlodipine:** Calcium channel blockers should be used with close monitoring, including close follow-up of fluid status, electrolytes, renal function, and blood pressure in patients with heart failure. Valsartan: Dosage reduction and/or discontinuation of the diuretic and/or valsartan may be required. **Hypersensitivity Reaction:** Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma. **Systemic Lupus Erythematosus:** Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus. **Electrolytes and Metabolic Imbalances:** Amlodipine -Valsartan - Hydrochlorothiazide: Monitor serum electrolytes periodically based on Exval-AH use and other factors such as renal function, other medications, or history of prior electrolyte imbalances. **Hydrochlorothiazide:** All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Hyperuricemia may occur or frank gout may be precipitated in certain patients. n diabetic patients, dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy. If progressive renal impairment becomes evident, consider withholding or discontinuing Exval-AH therapy or substituting other antihypertensive therapy. Thiazides have been REPORTED to cause hypomagnesemia, hypocalcaemia. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy. Acute Myopia and Secondary Angle-Closure Glaucoma: Hydrochlorothiazide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angleclosure 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.

ADVERSE REACTIONS: Adverse reactions that occurred with Exval-AH are listed below. It cannot be determined whether these events were causally related to Exval-AH. Tachycardia, Vertigo, tinnitus, blurred Vision, diarrhea, abdominal pain upper, vomiting, abdominal pain, tooth-ache, dry mouth, gastritis, haemorrhoids, asthenia, non-cardiac chest pain, chills, malaise, upper respiratory tract infection, bronchitis, influenza, pharyngitis, tooth abscess, gastroenteritis viral, respiratory tract infection, rhinitis, urinary tract infection, back injury, contusion, joint sprain, procedural pain, blood uric acid increased, blood creatine phosphokinase increased, weight decreased, hypokalaemia, diabetes mellitus, hyperlipidemia, hyponatremia, pain in extremity, arthralgia, musculoskeletal pain, muscular, weakness, musculoskeletal weakness, musculoskeletal stiffness, joint swelling, neck pain, osteoarthritis, tendonitis, parasthesia, somnolence, syncope, carpal tunnel syndrome, disturbance in attention, dizziness postural, dysgeusia, head discomfort, lethargy, sinus headache, tremor, anxiety, depression, insomnia, pollakiuria, erectile dysfunction, dyspnea, nasal congestion, cough, pharyngolaryngeal pain, pruritus, hyperhidrosis, night sweats, rash, hypotension Isolated cases of the following clinically notable adverse reactions were also observed in clinical trials: anorexia, constipation, dehydration, dysuria, increased appetite, viral infection.

DOSAGE AND ADMINISTRATION: General Considerations: Dose once-daily. The dosage may be increased after two weeks of therapy. The full blood pressure lowering effect was achieved 2 weeks after being on the maximal dose of Exval-AH. The maxi-mum recommended dose of Exval-AH is 10/320/25 mg. No initial dosage adjustment is required for elderly patients. **Renal impairment:** The usual regimens of therapy with Exval-AH may be followed if the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so avoid use of Exval-AH. **Hepatic impairment:** Avoid Exval-AH in patients with severe hepatic impairment. In patients with lesser degrees of hepatic impairment, monitor for worsening of hepatic or renal function and adverse reactions. **Add-on / Switch Therapy:** Exval-AH may be used for patients not adequately controlled on any two of the following antihypertensive classes: calcium channel blockers, angiotensin receptor blockers, and diuretics. A patient who experiences dose-limiting adverse reactions to an individual component while on any dual combination of the components of Exval-AH may be switched to Exval-AH containing a lower dose of that component to achieve similar blood pressure reductions. **Replacement Therapy:** Exval-AH may be substituted for the individually titrated components. Method of administration Exval-AH may be administered with or without food. **Overdose:** The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. **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.

INSTRUCTIONS

Dosage as directed by the physician. Store at 20°C - 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®-AH 5mg/160mg/12.5mg Tablets U.S.P. : Available in 2 X 7's & 4 X 7's Alu/Alu Blister pack of Tablets.
Exval®-AH 5mg/160mg/25mg Tablets U.S.P. : Available in 2 X 7's & 4 X 7's Alu/Alu Blister pack of Tablets.
Exval®-AH 10mg/160mg/12.5mg Tablets U.S.P. : Available in 2 X 7's & 4 X 7's Alu/Alu Blister pack of Tablets.
Exval®-AH 10mg/160mg/25mg Tablets U.S.P. : Available in 2 X 7's & 4 X 7's Alu/Alu Blister pack of Tablets.
Exval®-AH 10mg/320mg/25mg Tablets U.S.P. : Available in 2 X 7's Alu/Alu Blister pack of Tablets.

اعلامات/طریقہ استعمال:

ایکسویل-اے چ ان مریضوں کے لئے تجویز کردہ ہے جن میں بنیادی ہائی بلڈ پریشر کا ایملو ڈیپائینا اور ولسارٹن کی مجموعی تھراپی سے افاقہ نہ ہو سکے۔

عمومی خوراک: ایک ٹیبلٹ روزانہ ہے۔ایکسویل اے ایچ ٹیبلٹ کھانے کے ساتھ یا بغیر کھانے کے لی جاسکتی ہے۔

تھراپی کے اسے ۲ ہفتے بعد خوراک ڈاکٹر کی ہدایت کے مطابق بڑھائی جاسکتی ہے جو کہ ۱۰ ملی گرام/۳۲۰ ملی گرام/۲۵ ملی گرام یومیہ ہے۔

مضر اثرات: اختلاج قلب، الیکٹرولائٹس میں کمی، ہاتھوں، ٹخنوں اور پاؤں میں سوجن، سر درد اور چکر کمزوری۔

احتیاطی تدابیر:

حاملہ خواتین ہرگز استعمال نہ کریں۔میوکارڈئیل انفارکشن اور انجائنا ہونے کا خطرہ موجود ہے۔

گردے کے مریض احتیاط سے استعمال کریں۔شدید جگر کی خرابی کے مریض استعمال نہ کریں۔

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

۲۰ سے 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۔

For detailed information:

Genix Pharma (Pvt.) Ltd.

44,45-B, Korangi Creek Road, Karachi-75190, Pakistan.
UAN: +92-21-111-10-10-11, **Email:** info@genixpharma.com

ISO 9001:2015 ISO 14001:2015 ISO 45001:2018

www.genixpharma.com