Exval®-H 80mg/12.5mg

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

ایکسویل-ایچ ۸۰ ملی گرام/ ۱۲.۵ ملی گرام

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

QUALITATIVE AND QUANTITATIVE COMPOSITION

Exval®-H 80mg / 12.5mg Tablets

Each film-coated tablet contains:
Valsartan U.S.P. 80mg
Hydrochlorothiazide U.S.P. 12.5mg

WARNING: FETAL TOXICITY

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

DESCRIPTION

Exval-H (Valsartan and Hydrochlorothiazide, U.S.P.) is a combination of valsartan, an orally active, specific angiotensin II receptor blocker (ARB) acting on the AT1receptor subtype, and hydrochlorothiazide, a diuretic.

CLINICAL PHARMACOLOGY

Mechanism of Action: 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. **Hydrochlorothiazide:** It 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. **Pharmacodynamics: Valsartan:** Valsartan inhibits the pressor effect of angiotensin II infusions. An oral dose of 80 mg inhibits the pressor effect by about 80% at peak with approximately 30% inhibition persisting for 24 hours. Minimal decreases in plasma aldosterone were observed after administration of valsartan; very little effect on serum potassium was observed. **Hydrochlorothiazide:** After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours. **Pharmacokinetics: Valsartan:** Valsartan peak plasma concentration is reached 2 to 4 hours after dosing. Valsartan shows bi-exponential decay kinetics following intravenous administration, with an average elimination half-life of about 6 hours. Absolute bioavailability for the capsule formulation 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%. AUC and Cmax values of valsartan increase approximately linearly with increasing dose over the clinical dosing range. Valsartan does not accumulate appreciably in plasma following repeated administration. **Hydrochlorothiazide:** The estimated absolute bioavailability of hydrochlorothiazide after oral administration is about 70%. Peak plasma hydrochlorothiazide concentrations (Cmax) are reached within 2 to 5 hours after oral administration. There is no clinically significant effect of food on the bioavailability of hydrochlorothiazide. Hydrochlorothiazide binds to albumin (40% to 70%) and distributes into erythrocytes. Following oral administration, plasma hydrochlorothiazide concentrations decline bi-exponentially, with a mean distribution half-life of about 2 hours and an elimination half-life of about 10 hours. **Exval®-H:** Exval-H may be administered with or without food. **Distribution: Valsartan:** The steady state volume of distribution of valsartan after intravenous administration is small (17 L), indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (95%), mainly serum albumin. **Metabolism: Valsartan:** The primary metabolite, accounting for about

9% of dose, is valeryl 4-hydroxy valsartan. **Hydrochlorothiazide:** It is not metabolized. **Excretion: Valsartan:** Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). **Hydrochlorothiazide:** About 70% of an orally administered dose of hydrochlorothiazide is eliminated in the urine as unchanged drug.

INDICATIONS AND USAGE

Exval-H is indicated for the treatment of hypertension, to lower blood pressure:

•In patients not adequately controlled with 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

Exval®-H is contraindicated in patients who are hypersensitive to any component of this product. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs. Do not coadminister aliskiren with Exval-H in patients with diabetes. Avoid use of aliskiren with Exval-H in patients with renal impairment (GFR < 60 mL/min).

INTERACTIONS

Valsartan-Hydrochlorothiazide: Lithium: Monitoring of lithium levels is required as can cause lithium toxicity. **Valsartan:** The valsartan-atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone. **Transporters:** Rifampin, cyclosporine or ritonavir may increase the systemic exposure to valsartan. **NSAIDS including COX-2 Inhibitors:** Monitor renal function periodically in patients receiving valsartan and NSAID therapy as may result in deterioration of renal function in patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function. Closely monitor when taking with Exval-H. **Potassium:** If comedication is considered necessary, monitoring of serum potassium is advisable. **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. **Hydrochlorothiazide:** When administered concurrently, the following drugs may interact with thiazide diuretics: **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 gout-type complications. **Drugs that alter gastrointestinal motility:** The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g., atropine, biperiden). 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 myelosuppressive effects. **Antidiabetic drugs:** Dosage adjustment of antidiabetic may be required. **Cholestyramine and colestipol:** Reduced absorption of thiazides occur when these drugs are taken before hydrochlorothiazide. **Hydrochlorothiazide: 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. Caution with digoxin or other digitalis glycosides (medicines used to treat heart problems)

USE IN SPECIFIC POPULATION

Pregnancy: Category D: When pregnancy is detected, discontinue Exval-H as soon as possible as associated with neonatal morbidity and death. **Nursing Mothers:** For valsartan, its not known but hydrochlorothiazide is excreted in human milk. **Pediatric Use:** Safety and effectiveness of Exval®-H in pediatric patients have not been established. The

use of Valsartan HCT tablets in children and adolescents (below the age of 18 years) is not recommended. **Neonates with a history of in utero exposure to Exval®-H:** 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.**Renal Impairment:** Safety and effectiveness of Exval-H in patients with severe renal impairment (CrCl ≤ 30 mL/min) have not been established. No dose adjustment is required in patients with mild (CrCl 60 to 90 mL/min) or moderate (CrCl 30 to 60 mL/min) renal impairment.

Hepatic Impairment: Valsartan: No dose adjustment is necessary for patients with mild-to-moderate liver disease. No dosing recommendations can be provided for patients with severe liver disease. **Hydrochlorothiazide:** Minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.

PRECAUTIONS

Fetal Toxicity: Use of drugs acting on the RAS during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. **Hypotension in Volume- and/or Salt-Depleted Patients:** Excessive reduction of blood pressure was rarely seen (0.7%) in patients with uncomplicated hypertension treated with Exval-H in controlled trials. **Impaired Renal Function:** Acute renal failure can be caused by drugs that inhibit the RAS and by diuretics. **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 may cause exacerbation or activation of systemic lupus erythematosus. **Lithium Interaction:** Increases in serum lithium concentrations and lithium toxicity have been reported. **Potassium Abnormalities:** Hydrochlorothiazide can cause hypokalemia and hyponatremia. Hypomagnesemia can result in hypokalemia which appears difficult to treat despite potassium repletion. If hypokalemia is accompanied by clinical signs (e.g., muscular weakness, paresis, or ECG alterations), Exval-H should be discontinued. **Acute Myopia and Secondary Angle-Closure Glaucoma:** Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. **Metabolic Disturbances:** Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides. It also raises 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 receiving Exval-H. **Sensitivity of the skin to sun:** It may cause increased sensitivity of the skin to sun. **Hyperaldosteronism:** If you suffer from hyperaldosteronism, use of Valsartan HCT tablets is not recommended.

Driving and using machines: Caution should be taken as may occasionally cause dizziness and affect the ability to concentrate. **Valsartan HCT tablets contains lactose:** Incase of intolerance to some sugars, contact your doctor before taking it. **Valsartan HCT tablets contain soya oil:** If you are allergic to peanut or soya, do not take this medicinal product. **Alcohol:** Alcohol may make your blood pressure fall more and/or increase the risk of you becoming dizzy or feeling faint. Caution with sleeping pills, anesthetics, medicines that may increase blood sugar levels, such as diazoxide or beta blockers cytotoxic medicines, such as methotrexate or cyclophosphamide, amantadine, tubocurarine, cyclosporine is required. If you have diabetes, gout, high levels of cholesterol or fats in your blood, caution should be taken.

ADVERSE REACTIONS

Palpitation, tachycardia, tinnitus , vertigo, dyspepsia, diarrhea, flatulence, dry mouth, nausea, abdominal pain, vomiting, asthenia, chest pain, peripheral edema and pyrexia, bronchitis, influenza, gastroenteritis, sinusitis, upper respiratory tract infection, and urinary tract infection, arthralgia, muscle cramps, myalgia, and pain in extremity, paresthesia, and somnolence, pollakiuria, erectile dysfunction, respiratory, dyspnea , pharyngolaryngeal pain, sinus congestion, hyperhidrosis and rash, hypotension, angioedema, (such as swollen face, tongue or pharynx, difficulty in swallowing, hives and difficulties in breath-

ing). **Side effects include:** Cough, low blood pressure, light-headedness, dehydration (with symptoms of thirst, dry mouth and tongue, infrequent urination, dark colored urine, dry skin), tiredness, tingling or numbness, blurred vision, noises (e.g. hissing, buzzing) in ears, diarrhea, joint pain.

DOSAGE AND ADMINISTRATION

Exval-H tablets can be taken with or without food. **General Considerations:** The recommended dose of Valsartan /Hydrochlorothiazide is once a day. Dose titration with the individual components is recommended. In each case up-titration of individual components to the next dose should be followed in order to reduce the risk of hypotension and other adverse events. The usual starting dose of Exval-H 80mg/12.5mg or 160mg/12.5 mg once daily depending on the clinical need. The dosage can be increased after 1 to 2 weeks of therapy to a maximum 320mg/25mg once daily as needed to control blood pressure. Maximum antihypertensive effects are attained within 2 to 4 weeks after a change in dose.

Add-On Therapy: A patient whose blood pressure is not adequately controlled with valsartan (or another ARB) alone or hydrochlorothiazide alone may be switched to combination therapy with Exval®-H. A patient who experiences dose-limiting adverse reactions on either component alone may be switched to Exval-H containing a lower dose of that component in combination with the other to achieve similar blood pressure reductions. The clinical response to Exval-H should be subsequently evaluated and if blood pressure remains uncontrolled after 3 to 4 weeks of therapy, the dose may be titrated up to a maximum of 320mg / 25mg.

Replacement Therapy: Exval®-H may be substituted for the titrated components.

Initial Therapy: Exval®-H is not recommended as initial therapy in patients with intravascular volume depletion. **Use with Other Antihypertensive Drugs:** Exval-H may be administered with other antihypertensive agents. **Overdosage:** Valsartan–Hydrochlorothiazide: Limited data is available related to overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. Depressed level of consciousness, circulatory collapse and shock have been reported. If symptomatic hypotension should occur, supportive treatment should be instituted. Valsartan is not removed from the plasma by dialysis. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

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®-H 80mg/12.5mg (Valsartan 80mg / Hydrochlorothiazide 12.5mg) Tablets U.S.P. are available in Alu-Alu blister pack of 28's.

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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