Co-Valid™

کو-ویلڈ

[VALSARTAN + HYDROCHLOROTHIAZIDE]

Co-Valid 80/12.5
Each film coated tablet contains valsartan 80mg and hydrochlorothiazide 12.5 mg.....USP
Co-Valid 160/12.5
Each film coated tablet contains valsartan 160 mg and hydrochlorothiazide 12.5 mg.....USP
Co-Valid 160/25
Each film coated tablet contains valsartan 160 mg and hydrochlorothiazide 25 mg.....USP

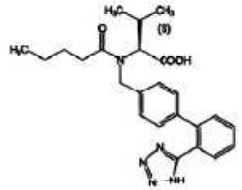
WARNING

AVOID USE IN PREGNANCY
When pregnancy is detected, discontinue Co-Valid (Valsartan and Hydrochlorothiazide) as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. [See WARNINGS AND PRECAUTIONS]

DRUG DESCRIPTION:

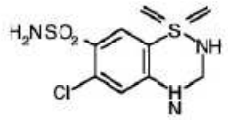
(Valsartan and hydrochlorothiazide, USP) is a combination of valsartan an orally active, specific angiotensin II receptor blocker (ARB) acting on the AT1 receptor subtype, and hydrochlorothiazide, a diuretic.

Valsartan, a nonpeptide molecule, is chemically described as N-(1-oxopentyl)-N-[[2-(1 H-tetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-L-Valine. Its empirical formula is $C_{24}H_{29}N_5O_3$. Its molecular weight is 435.5 and its structural formula is



Valsartan is a white to practically white fine powder. It is soluble in ethanol and methanol and slightly soluble in water. Hydrochlorothiazide USP is a white, or practically white, practically odorless, crystalline powder. It is slightly soluble in water freely soluble in sodium hydroxide solution, in n-butylamine, and in dimethylformamide; sparingly soluble in methanol; and insoluble in ether, in chloroform, and in dilute mineral acids. Hydrochlorothiazide is chemically described as 6-chloro-3, 4-dihydro-2H-1, 2, 4-benzothiadiazine-7-sulfonamide1, 1-dioxide.

Hydrochlorothiazide is a thiazide diuretic. Its empirical formula is $C_7H_8ClN_3O_4S_2$, its molecular weight is 297.73, and its structural formula is



CLINICAL PHARMACOLOGY:
Mechanism of Action

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. 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. Its action is therefore independent of the pathways for angiotensin II synthesis.

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte re-absorption, 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.

The mechanism of the antihypertensive effect of thiazides is unknown.

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. No information on the effect of larger doses is available.

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%-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

Thiazide diuretics are eliminated by the kidney, with a terminal half-life of 5-15 hours.

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 impairment. Consequently, dose adjustment is not required in patients with mild-to-moderate renal dysfunction. No studies have been performed in patients with severe impairment of renal function (creatinine clearance < 10 mL/min). Valsartan is not removed from the plasma by hemodialysis. In the case of severe renal disease, exercise care with dosing of valsartan.

Hepatic Insufficiency: On average, patients with mild-to-moderate chronic liver disease have twice the exposure (measured by AUC values) to valsartan of healthy volunteers (matched by age, sex, and weight). In general, no dosage adjustment is needed in patients with mild-to-moderate liver disease. Care should be exercised in patients with liver disease [See DOSAGE AND ADMINISTRATION].

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.

Hydrochlorothiazide: Hydrochlorothiazide crosses the placental but not the blood brain barrier and is excreted in breast milk.

Metabolism

Valsartan: The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan. The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes.

Hydrochlorothiazide: 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). The recovery is mainly as uncharged drug, with only about 20% of dose recovered as metabolites.

Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance).

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.

INDICATIONS:

Co-Valid (valsartan and hydrochlorothiazide, USP) is indicated for the treatment of hypertension.

Co-Valid (valsartan and hydrochlorothiazide) may be used in patients whose blood pressure is not adequately controlled on monotherapy.

Co-Valid (valsartan and hydrochlorothiazide) may be used as initial therapy in patients who are likely to need multiple drugs to achieve blood pressure goals.

The choice of Co-Valid (valsartan and hydrochlorothiazide) as initial therapy for hypertension should be based on an assessment of potential benefits and risks.

DOSAGE AND ADMINISTRATION:

General Considerations
The side effects of valsartan are generally rare and appear independent of dose. Those of hydrochlorothiazide are a mixture of dose-dependent (primarily hypokalemia) and dose independent phenomena (e.g. pancreatitis), the former much more common than the latter.

Dose once daily. Maximum antihypertensive effects are attained within 2 to 4 weeks after a change in dose.

Co-Valid (valsartan and hydrochlorothiazide) may be administered with or without food.

Co-Valid (valsartan and hydrochlorothiazide) may be administered with other antihypertensive agents.

Renal Impairment: The usual regimens of therapy with Co-Valid (valsartan and hydrochlorothiazide) may be followed as long as the patient's creatinine clearance is >30mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so Co-Valid (valsartan and hydrochlorothiazide) is not recommended.

Hepatic Impairment: Care should be exercised with dosing of Co-Valid (valsartan

and hydrochlorothiazide) in patients with hepatic impairment. Start with a low dose and titrate slowly in patients with hepatic impairment.

SIDE EFFECTS:

Hypertension
Co-Valid (valsartan and hydrochlorothiazide, USP) has been evaluated for safety in more than 5,700 patients, including over 990 treated for over 6 months and over 370 for over 1 year. Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The overall incidence of adverse reactions with Co-Valid (valsartan and hydrochlorothiazide) was comparable to placebo.

The overall frequency of adverse reactions was neither dose-related nor related to gender, age, or race. In controlled clinical trials, discontinuation of therapy due to side effects was required in 2.3% of valsartan-hydrochlorothiazide patients and 3.1% of placebo patients. The most common reasons for discontinuation of therapy with Co-Valid (valsartan and hycrochlorothiazide) were headache and dizziness.

Dose-related orthostatic effects were seen in fewer than 1% of patients. In individual trials, a dose-related increase in the incidence of dizziness was observed in patients treated with Co-Valid (valsartan and hydrochlorothiazide).

Other adverse reactions that have been reported with valsartan hydrochlorothiazide (>0.2% of valsartan-hydrochlorothiazide patients in controlled clinical trials) without regard to causality, are listed below:

Cardiovascular: Palpitations and tachycardia
Ear and Labyrinth: Tinnitus and vertigo
Gastrointestinal: Dyspepsia, diarrhea, flatulence, dry mouth, nausea, abdominal pain, abdominal pain upper, and vomiting.
General and Administration Site Conditions: Asthenia, chest pain, fatigue, peripheral edema and pyrexia.
Infections and Infestations: Bronchitis, bronchitis acute, influenza, gastroenteritis, sinusitis, upper respiratory tract infection and urinary tract infection.
Investigations: Blood urea increased.
Musculoskeletal: Arthralgia, back pain, muscle cramps, myalgia, and pain in extremity
Nervous System: Dizziness postural, paresthesia, and somnolence.
Psychiatric: Anxiety and insomnia.
Renal and Urinary: Pollakiuria.
Reproductive System: Erectile dysfunction.
Respiratory, Thoracic and Mediastinal: Dyspnea, cough, nasal congestion, pharyngolaryngeal pain and sinus congestion.
Skin and Subcutaneous Tissue: Hyperhidrosis and rash.
Hydrochlorothiazide: Other adverse reactions that have been reported with hydrochlorothiazide, without regard to causality, are listed below:
Body As A Whole: weakness;
Digestive: pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation;
Hypersensitivity: purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions;
Metabolic: hyperglycemia, glycosuria, hyperuricemia;
Musculoskeletal: muscle spasm;
Nervous System/Psychiatric: restlessness;
Renal: renal failure, renal dysfunction, interstitial nephritis;
Skin: erythema multiform including Stevens Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis;
Special Senses: transient blurred vision, xanthopsia.

DRUG INTERACTIONS:

Valsartan
No clinically significant pharmacokinetic interactions were observed when valsartan was co-administered with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The valsartan - atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone.
Co-administration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.

CYP 450 Interactions: The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes. The inhibitory or induction potential of valsartan on CYP 450 is also unknown.

Hydrochlorothiazide
When administered concurrently, the following drugs may interact with thiazide diuretics:

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.

Other Antihypertensive drugs - Additive effect or potentiation.

Cholestyramine and Colestipol Resins - Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43% respectively.

Corticosteroids, ACTH - Intensified electrolyte depletion, particularly hypokalemia.

Pressor Amines (e.g., norepinephrine) - Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal Muscle Relaxants, Nondepolarizing (e.g., tubocurarine) - Possible increased responsiveness to the muscle relaxant.

Lithium - Should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with Co-Valid (valsartan and hydrochlorothiazide).

Nonsteroidal Anti-Inflammatory Drugs - In some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when Co-Valid (valsartan and hydrochlorothiazide) and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carbamazepine - May lead to symptomatic hyponatremia.

WARNING AND PRECAUTIONS:

Fetal/Neonatal Morbidity and Mortality
Co-Valid (valsartan and hydrochlorothiazide) can cause fetal harm 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.

Intrauterine exposure to thiazide diuretics is associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

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 Co Valid (valsartan and hydrochlorothiazide) in controlled trials. In patients with an activated renin-angiotensin system, such as volume and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur.

Impaired Hepatic Function
Hycrochlorothiazide: Thiazide diuretics should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Valsartan: 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). Care should be exercised in administering valsartan to these patients.

Impaired Renal Function
Valsartan: As a consequence of inhibiting the renin-angiotensin aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive 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.

Hycrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

OVERDOSE.

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 levels of consciousness, circulatory collapse and shock have been reported. If symptomatic hypotension should occur, supportive treatment should be instituted.

CONTRAINDICATIONS:

Co-Valid (valsartan and hydrochlorothiazide, USP) 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.

HOW SUPPLIED / STORAGE AND HANDLING:
Co-Valid (valsartan and hycrochlorothiazide, USP) is available as film coated tablets containing valsartan/hycrochlorothiazide 80/12.5mg, 160/12.5mg and 160/25mg.

Store below 30°C
Protect from light, heat and moisture.
Use as directed by registered physician.
Keep all medicine out of reach of children.

ہدایات
صرف رجسٹرڈ ڈاکٹر کے نسخہ پر ہی فروخت کی جائے۔
گرمی، روشنی اور نمی سے محفوظ ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
ڈاکٹری ہدایت کے مطابق استعمال کریں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

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