120x280mm

Nebix-V™

(Nebivolol + Valsartan)

Highnoon

Composition:
Nebix-V 5mg/80mg Tablet:
Each film-coated tablet contains:
Nebivolol (as HCl) 5mg
Valsartan 80mg

DESCRIPTION
Nebix-V (Nebivolol and Valsartan) is available as tablets for oral administration. Each tablet contains 5.45mg of nebivolol hydrochloride, which is equivalent to 5mg of nebivolol free base, and 80mg of valsartan.

MECHANISM OF ACTION
Nebivolol
Nebivolol is a β-adrenergic receptor blocking agent. It has vasodilating activity, which appears to be due to a direct action on the endothelium, possibly involving nitric oxide release. It is reported to lack intrinsic sympathomimetic and membrane stabilizing activity.
The mechanism of action of the antihypertensive response of nebivolol has not been definitively established. Possible factors that may be involved are decreased heart rate, decreased myocardial contractility, decreased sympathetic activity, suppression of renin activity, and vasodilation and decreased peripheral vascular resistance.

Valsartan
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 AT_1 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. There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis.
Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because valsartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.
Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of valsartan on blood pressure.

PHARMACOKINETICS
Food had a minor impact on the pharmacokinetics of nebivolol, nebivolol glucuronides and valsartan. Nebix-V (Nebivolol and Valsartan) may be administered without regard to meals.

Nebivolol
Nebivolol is rapidly absorbed after oral doses. It is extensively metabolized in the liver by alicyclic and aromatic hydroxylation, N-dealkylation and glucuronidation. The hydroxy metabolites are reported to be active. The rate of aromatic hydroxylation by cytochrome P450 isoenzyme CYP2D6 is subject to genetic polymorphism, and bioavailability and half-life vary widely. In fast metabolizers the elimination half-life of nebivolol is about 10 hours and that of hydroxy metabolites is about 24 hours. Peak plasma concentration of unchanged drug plus active metabolites are 1.3 to 1.4 times higher in slow metabolizers and the half-lives of nebivolol and its hydroxy metabolites are prolonged. Nebivolol is about 98% bound to plasma proteins. It has high lipid solubility. It is excreted in the urine and feces, almost entirely as metabolites.

Valsartan
Valsartan is rapidly absorbed after oral doses, with a bioavailability of about 23% when given as a tablet and about 39% when given as a solution. Peak plasma concentrations of valsartan occur 2 to 4 hours after tablets and 1 to 2 hours after oral solutions. It is between 94 and 97% bound to plasma proteins. Valsartan is not significantly metabolized and is excreted mainly via the bile as unchanged drug. The terminal elimination half-life is about 6 hours. Following an oral dose about 83% excreted in the feces and 13% in the urine.

INDICATIONS AND USAGE
Nebix-V (Nebivolol and Valsartan) is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. It may be used alone or in combination with other antihypertensive agents.

DOSAGE AND ADMINISTRATION
As initial therapy and in patients not adequately controlled on valsartan 80mg or nebivolol up to and including 10mg, the recommended dose of Nebix-V is one tablet, 5mg / 80mg (nebivolol / valsartan) taken orally once daily. Maximum antihypertensive effects are attained within 2 to 4 weeks. Increasing the dose of Nebix-V does not result in any meaningful further blood pressure reduction.
Nebix-V may be substituted for its components in patients already receiving 5mg nebivolol and 80mg valsartan.

CONTRAINDICATIONS
It is contraindicated in the following conditions:
- Severe bradycardia
- Heart block greater than first degree
- Patients with cardiogenic shock
- Decompensated cardiac failure
- Sick sinus syndrome (unless a permanent pacemaker is in place)
- Patients with severe hepatic impairment (Child-Pugh >B)
- Patients who are hypersensitive to any component of this product.
- Do not co-administer aliskiren with this combination (Nebivolol and Valsartan) in patients with diabetes.

WARNINGS AND PRECAUTIONS
Fetal Toxicity
Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue this combination (Nebivolol and Valsartan) as soon as possible.

Hypotension
In patients with an activated renin-angiotensin-aldosterone system, such as volume-and/or salt-depleted patients (e.g., those receiving high doses of diuretics), symptomatic hypotension may occur in patients receiving this combination (Nebivolol and Valsartan). Correct these conditions prior to administration of this combination (Nebivolol and Valsartan) or start the treatment under close medical supervision. If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

Abrupt Cessation of Therapy
Do not abruptly discontinue this combination (Nebivolol and Valsartan) in patients with coronary artery disease. Severe exacerbation of angina, myocardial infarction and ventricular arrhythmias have been reported in patients with coronary artery disease following the abrupt discontinuation of therapy with β-blockers. Myocardial infarction and ventricular arrhythmias may occur with or without preceding exacerbation of the angina pectoris. As with other β-blocker therapies, when discontinuation of this combination (Nebivolol and Valsartan) is planned, carefully observe and advise patients to minimize physical activity. Taper nebivolol using monotherapy over 1 to 2 weeks when possible. If the angina worsens re-start nebivolol promptly, at least temporarily.

Cardiac Failure
Worsening heart failure or fluid retention may occur during nebivolol therapy because of its ß-blocking effects. Consider diuretic therapy and treat heart failure appropriately, according to current guidelines.

Bronchospastic Diseases
In general, patients with bronchospastic diseases should not receive β-blockers.

Anesthesia and Major Surgery
Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery, however the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures. Monitor patients closely when anesthetic agents which depress myocardial function, such as ether, cyclopropane, and trichloroethylene, are used.

Diabetes and Hypoglycemia
β-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nonselective β-blockers may potentiate insulin-induced hypoglycemia and delay recovery of serum glucose levels. It is not known whether nebivolol has these effects. Advise patients subject to spontaneous hypoglycemia and diabetic patients receiving insulin or oral hypoglycemic agents about these possibilities.

Thyrotoxicosis
β-blockers may mask clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of βblockers may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate a thyroid storm.

Peripheral Vascular Disease
β-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease.

Non-dihydropyridine Calcium Channel Blockers
Because of significant negative inotropic and chronotropic effects in patients treated with β-blockers and calcium channel blockers of the verapamil and diltiazem type, monitor heart rate and blood pressure in patients treated concomitantly with these agents.

Impaired Renal Function
Changes in renal function including acute renal failure can be caused by drugs that inhibit the renin-angiotensin system and by diuretics. Patients whose renal function may depend in part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing acute renal failure on Valsartan. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on Valsartan.

Risk of Anaphylactic Reactions
While taking β-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reactions.

Pheochromocytoma
In patients with known or suspected pheochromocytoma, initiate a α-blocker prior to the use of any β-blocker.

Hyperkalemia
Some patients with heart failure have developed increases in potassium. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Discontinuation of Valsartan may be required.

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ADVERSE REACTIONS
The reported adverse events associated with valsartan are headache, dizziness, hypotension, hyperkalemia, upper respiratory infection, cough, diarrhea, rhinitis, sinusitis, nausea, pharyngitis, edema, arthralgia, viral infection, fatigue, abdominal pain, allergic reaction, asthenia, palpitations, pruritus, rash, constipation, dry mouth, dyspepsia, flatulence, back pain, muscle cramps, myalgia, anxiety, insomnia, paresthesia, hepatitis, somnolence, dyspnea, vertigo, impotence, chest pain, syncope, anorexia, vomiting, angioedema, hyperkalemia, liver transaminase elevations, elevations in creatinine, elevations in potassium, impaired renal function , increases in blood urea nitrogen, renal failure, alopecia, bullous dermatitis, vasculitis, thrombocytopenia, rhabdomyolysis, and blurred vision.
The reported adverse events associated with nebivolol are atrioventricular block (both second and third degree), myocardial infarction, somnolence, syncope, vertigo, Raynaud's phenomenon, peripheral ischemia/claudication, thrombocytopenia, pruritus, psoriasis, various rashes and skin disorders, vomiting, abnormal hepatic function (including increased AST, ALT and bilirubin), hypersensitivity (including urticaria, allergic vasculitis and rare reports of angioedema), acute renal failure, acute pulmonary edema, bronchospasm and erectile dysfunction.

DRUG INTERACTIONS
Nebivolol
- Avoid concomitant use of nebivolol with CYP2D6 inhibitors (quinidine, propafenone, fluoxetine, paroxetine, etc.).
- Do not use nebivolol with other β-blockers. Closely monitor patients receiving catecholamine-depleting drugs, such as reserpine or guanethidine, because the added β-blocking action of nebivolol may produce excessive reduction of sympathetic activity. In patients who are receiving nebivolol and clonidine, discontinue nebivolol for several days before the gradual tapering of clonidine.
- Concomitant use of digitalis glycoside can increase the risk of bradycardia. Both digitalis glycosides and β-blockers slow atrioventricular conduction and decrease heart rate. Monitor for bradycardia.
- Nebivolol can exacerbate the effects of myocardial depressants or inhibitors of AV conduction, such as certain calcium antagonists (particularly of the phenylalkylamine [verapamil] and benzothiazepine [diltiazem] classes), or antiarrhythmic agents, such as disopyramide. Monitor for effects on heart rate and cardiac conduction.

Valsartan
- Concomitant use of valsartan with other agents that block the renin-angiotensin system, potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, salt substitutes containing potassium or other drugs that may increase potassium levels (e.g., heparin) may lead to increases in serum potassium (hyperkalemia) and in heart failure patients to increases in serum creatinine. Monitor serum potassium in such patients.
- In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including valsartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving valsartan and NSAID therapy. The antihypertensive effect of angiotensin II receptor antagonists, including valsartan may be attenuated by NSAIDs including selective COX-2 inhibitors.
- 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. Most patients receiving the combination of two RAS inhibitors do not obtain any additional benefit compared to monotherapy. In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function and electrolytes in patients on Valsartan and other agents that affect the RAS. Do not co-administer aliskiren with this combination (Nebivolol / and Valsartan) in patients with diabetes.
- Do not coadministered aliskiren with Valsartan in patients with diabetes. Avoid use of aliskiren with Valsartan in patients with renal impairment (GFR <60 mL/min).
- Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium angiotensin II receptor antagonists, including valsartan. Monitor serum lithium levels during concomitant use.
- Elevations in creatinine, decrease in hemoglobin & hematocrit, occasional elevation of liver chemistries, neutropenia, increase in serum potassium and blood urea nitrogen was observed in patients taking Valsartan. Proper monitoring and caution should be taken while using Valsartan.

USE IN SPECIFIC POPULATIONS
Pregnancy
Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue valsartan as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimesters of pregnancy. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.
There is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue valsartan, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to valsartan for hypotension, oliguria, and hyperkalemia.
Neonates of women with hypertension, who are treated with beta-blockers during pregnancy, may be at increased risk for hypotension, bradycardia, hypoglycemia, and respiratory depression. Observe newborns for symptoms of hypotension, bradycardia, hypoglycemia and respiratory depression and manage accordingly.

Nursing Mothers
There is no information regarding the presence of individual components of this combination (Nebivolol /Valsartan) in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for β-blockers to produce serious adverse reactions in nursing infants, especially bradycardia, and the potential for valsartan to affect postnatal renal development in nursing infants, advise a nursing woman not to breastfeed during treatment with this combination (Nabivolol and Valsartan).

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
There were no notable differences in efficacy or safety between older and younger patients.

Renal Impairment
Safety and effectiveness of this combination (Nebivolol and Valsartan) in patients with moderate and severe renal impairment (CrCl ≤60 mL/min) have not been established. No dose adjustment is required in patients with mild or moderate renal impairment.
It is not recommended as initial treatment in patients with severe renal impairment, because the recommended starting dose of nebivolol in this population, 2.5mg once daily, is lower than the dose of nebivolol contained in it.

Hepatic Impairment
No dose adjustment is necessary for patients with mild-to-moderate liver disease. No initial dosage adjustment is required for patients with mild hepatic impairment. This combination (Nebivolol and Valsartan) is not recommended as initial treatment in patients with moderate hepatic impairment, because the recommended starting dose of nebivolol, 2.5mg once daily, is not available. This combination (Nebivolol and Valsartan) is not recommended for use in patients with severe hepatic impairment.

OVERDOSAGE
Limited data are available related to overdosage of valsartan in humans. The most likely manifestations of overdosage would be peripheral vasodilation, 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. Valsartan is not removed from plasma by hemodialysis.
The most common signs and symptoms associated with nebivolol overdosage are bradycardia and hypotension. Other important adverse reactions reported with nebivolol overdose include cardiac failure, dizziness, hypoglycemia, fatigue and vomiting. Other adverse reactions associated with β-blocker overdose include bronchospasm and heart block. Because of extensive drug binding to plasma proteins, hemodialysis is not expected to enhance nebivolol clearance. If overdosage occurs, provide general supportive and specific symptomatic treatment. Supportive measures should continue until clinical stability is achieved. The half-life of low doses of nebivolol is 12-19 hours.

DOSAGE & INSTRUCTIONS
To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30ºC. Keep in a dry place. Protect from light.

PRESENTATION:
Nebix-V 5mg/80mg Tablets:
Alu. Alu. Blister Pack of 2 x 7's.

نیبِکس-وی™

(نیبی ولول + والسرٹان)

خوراک و ہدایات:

صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

Manufactured by
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www.highnoon-labs.com

Item Code No. 14001965