Nebix®
(Nebivolol)

Highnoon

COMPOSITION
Nebix 2.5mg Tablet:
Each film-coated tablet contains Nebivolol (as HCl) 2.5mg
Nebix 5mg Tablet:
Each film-coated tablet contains Nebivolol (as HCl) 5mg
Nebix 10mg Tablet:
Each film-coated tablet contains Nebivolol (as HCl) 10mg

DESCRIPTION
Nebix is a selective beta blocker agent.

MECHANISM OF ACTION
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, vasodilation and decreased peripheral vascular resistance.

PHARMACOKINETICS
Food had a minor impact on the pharmacokinetics of nebivolol. It may be administered without regard to meals.

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.

INDICATIONS AND USAGE
It 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.
- Stable mild and moderate chronic heart failure in addition to standard therapies in elderly patients 70 years old or above.

DOSAGE AND ADMINISTRATION
The dose must be individualized to the needs of the patient. For most patients, the recommended starting dose is 5 mg once daily, with or without food, as monotherapy or in combination with other agents. For patients requiring further reduction in blood pressure, the dose can be increased at 2-week intervals up to 40 mg. A more frequent dosing regimen is unlikely to be beneficial.

Renal Impairment
In patients with severe renal impairment (ClCr less than 30 mL/min) the recommended initial dose is 2.5 mg once daily; titrate up slowly if needed. It has not been studied in patients receiving dialysis.

Hepatic Impairment
In patients with moderate hepatic impairment, the recommended initial dose is 2.5 mg once daily; titrate up slowly if needed. It has not been studied in patients with severe hepatic impairment and therefore it is not recommended in that population.

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 Nebivolol and Valsartan combination in patients with diabetes.

WARNINGS AND PRECAUTIONS
Abrupt Cessation of Therapy
Do not abruptly discontinue Nebivolol 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 Nebivolol 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.

Angina and Acute Myocardial Infarction
It was not studied in patients with angina pectoris or who had a recent MI.

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

Anesthesia and Major Surgery
Because beta-blocker withdrawal has been associated with an increased risk of MI and chest pain, patients already on beta-blockers should generally continue treatment throughout the perioperative period. If it is to be continued perioperatively, monitor patients closely when anesthetic agents which depress myocardial function, such as ether, cyclopropane, and trichloroethylene, are used. 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. The β-blocking effects of nebivolol can be reversed by β-agonists, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Additionally, difficulty in restarting and maintaining the heartbeat has been reported with β-blockers.

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 β-blockers 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 increase 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.

Use with CYP2D6 Inhibitors
Nebivolol exposure increases with inhibition of CYP2D6. The dose of nebivolol may need to be reduced.

ADVERSE REACTIONS
The reported adverse events are: headache, nausea, bradycardia, abdominal pain, diarrhea, fatigue, chest pain, peripheral edema, dizziness, insomnia, dyspnea, rash, hypercholesterolemia increase in blood urea nitrogen, increase in uric acid, increase triglyceride, decrease HDL cholesterol, decrease in platelet count, abnormal hepatic function (including increase AST, ALT and bilirubin), acute pulmonary edema, acute renal failure, asthenia, paresthesia, atrioventricular block (both second and third degree), bronchospasm, erectile dysfunction, hypersensitivity (including urticaria, allergic vasciltis and rare reports of angioedema), hypotension, myocardial infarction, pruritus, psoriasis, Raynaud's phenomenon, peripheral ischemia/-claudication, somnolence, syncope, thrombocytopenia, various rashes and skin disorders, vomiting and vertigo.

DRUG INTERACTIONS
- 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.

USE IN SPECIFIC POPULATIONS
Pregnancy
Available data regarding use of nebivolol in pregnant women are insufficient to determine whether there are drug-associated risks of adverse developmental outcomes. There are risks to the mother and fetus associated with poorly controlled hypertension in pregnancy. The use of beta blockers during the third trimester of pregnancy may increase the risk of hypotension, bradycardia, hypoglycemia, and respiratory depression in the neonate. 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 nebivolol or its components 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, nebivolol is not recommended during nursing.

Paediatric Use
Safety and effectiveness in paediatric patients have not been established.

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

Heart Failure
If heart failure worsens consider discontinuation of nebivolol.

Renal impairment
Renal clearance of nebivolol is decreased in patients with severe renal impairment. It has not been studied in patients receiving dialysis.

Hepatic impairment
Metabolism of nebivolol is decreased in patients with moderate hepatic impairment. It has not been studied in patients with severe hepatic impairment.

OVERDOSAGE
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 overdose 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 AND 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 30°C. Keep in a dry place. Protect from light.

PRESENTATION
Nebix 2.5mg Tablets: Alu. Alu. Blister Pack of 1 x 14's.
Nebix 5mg Tablets: Alu. Alu. Blister Pack of 1 x 14's.
Nebix 10mg Tablets: Alu. Alu. Blister Pack of 1 x 14's.

نیبِکس®
(نیبی ولول)

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۔

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