ByVas®
(Nebivolol)

بائیوس

COMPOSITION
Each tablet contain:
Nebivolol (as hydrochloride)……...2.5mg
Nebivolol (as hydrochloride)…….....5mg
Nebivolol (as hydrochloride)…….....10mg
(As per innovator's specs.)

DESCRIPTION
Nebivolol is a β-adrenergic receptor blocking agent. The chemical name for the active ingredient in nebivolol tablets is (1RS,1'RS)-1,1'-[(2RS,2'SR)bis(6-fluoro-3,4-dihydro-2H-1-benzopyran-2-yl)]-2,2'-iminodiethanol hydrochloride. Nebivolol is a racemate composed of d-Nebivolol and l-Nebivolol with the stereochemical designations of [SRRR]-nebivolol and [RSSS]nebivolol, respectively. Nebivolol's molecular formula is ($C_{22}H_{25}F_2NO_4$•HCl).

CLINICAL PHARMACOLOGY

Mechanism of Action
The mechanism of action of the antihypertensive response of Nebivolol has not been definitively established. Possible factors that may be involved include: (1) decreased heart rate, (2) decreased myocardial contractility, (3) diminution of tonic sympathetic outflow to the periphery from cerebral vasomotor centers, (4) suppression of renin activity and (5) vasodilation and decreased peripheral vascular resistance.

Pharmacodynamics properties
In extensive metabolizers (most of the population) and at doses less than or equal to 10 mg, nebivolol is preferentially β1 selective. In poor metabolizers and at higher doses, nebivolol inhibits both β1 - and β2 - adrenergic receptors. Nebivolol lacks intrinsic sympathomimetic and membrane stabilizing activity at therapeutically relevant concentrations. At clinically relevant doses, Nebivolol does not demonstrate α 1-adrenergic receptor blockade activity. Various metabolites, including glucuronides, contribute to β-blocking activity.

Pharmacokinetics

Absorption
Absorption of Nebivolol is similar to an oral solution. The absolute bioavailability has not been determined. Mean peak plasma nebivolol concentrations occur approximately 1.5 to 4 hours post-dosing in EMs and PMs. Food does not alter the pharmacokinetics of nebivolol. Under fed conditions, nebivolol glucuronides are slightly reduced. Nebivolol may be administered without regard to meals.

Distribution
The in vitro human plasma protein binding of nebivolol is approximately 98%, mostly to albumin, and is independent of nebivolol concentrations.

Metabolism
Nebivolol is predominantly metabolized via direct glucuronidation of parent and to a lesser extent via N¬dealkylation and oxidation via cytochrome P450 2D6. Its stereospecific metabolites contribute to the pharmacologic activity.

Elimination
After a single oral administration of 14C-nebivolol, 38% of the dose is recovered in urine and 44% in feces and 67% in urine and 13% in feces. Essentially all nebivolol is excreted as multiple oxidative metabolites or their corresponding glucuronide conjugates.

Pharmacokinetics in special populations

Hepatic Disease
d-Nebivolol peak plasma concentration increased 3-fold, exposure (AUC) increases 10-fold, and the apparent clearance decreases by 86% in patients with moderate hepatic impairment (Child-Pugh Class B). No data is available in patients with severe hepatic impairment and nebivolol should be contraindicated for these patients.

Renal Disease
The apparent clearance of nebivolol is unchanged following a single 5 mg dose of Nebivolol in patients with mild renal impairment (ClCr 50 to 80 mL/min, n=7), and it was reduced negligibly inpatients with moderate (ClCr 30 to 50 mL/min, n=9), but clearance is reduced by 53% in patients with severe renal impairment (ClCr <30 mL/min, n=5). No data is available in patients on dialysis.

INDICATIONS
Nebivolol is indicated for the treatment of hypertension, to lower blood pressure. Nebivolol may be used alone or in combination with other antihypertensive agents.

DOSAGE AND ADMINISTRATION

Adult dosage

Hypertension
The dose of Nebivolol 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.

Dosage adjustment

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, the daily dose may cautiously. No data is available 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. No data is available in patients with severe hepatic impairment and therefore it is not recommended in that population.

Geriatric Patients
It is not necessary to adjust dose in geriatric patients, However, in view of the limited experience in patients above 75 years, caution must be exercised and these patients monitored closely.

CYP2D6 Polymorphism
No dose adjustments are necessary for patients who are CYP2D6 poor metabolizers.

CONTRAINDICATIONS
Nebivolol 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
- Metabolic acidosis
- Untreated phaeochromocytoma
- Severe peripheral circulatory disturbances.

WARNING AND PRECAUTIONS

Abrupt Cessation of Therapy
Do not abruptly discontinue Nebivolol therapy in patients with coronary artery disease. Severe exacerbation of angina, myocardial infarction and ventricular arrhythmias may be observed 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. Caution patients without overt coronary artery disease against interruption or abrupt discontinuation of therapy. As with other β-blockers, when discontinuation of Nebivolol is planned, carefully observe and advise patients to minimize physical activity. Taper Nebivolol over 1 to 2 weeks when possible. If the angina worsens or acute coronary insufficiency develops, re-start Nebivolol promptly, at least temporarily.

Angina and Acute Myocardial Infarction
No data is available for Nebivolol use 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 Nebivolol is to be continued perioperatively, monitor patients closely when anesthetic agents which depress myocardial function, such as ether, cyclopropane, and trichloroethylene, are used. If β-blocking therapy is withdrawn prior to major surgery, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures. 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 may be observed 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 chronoscopic effects in patients treated with β-blockers and calcium channel blockers of the verapamil and diltiazem type, monitor the ECG and blood pressure in patients treated concomitantly with these agents.

Impaired Renal Function
Renal clearance of nebivolol is decreased in patients with severe renal impairment. No data is available in patients receiving dialysis.

Impaired Hepatic Function
Metabolism of nebivolol is decreased in patients with moderate hepatic impairment. No data is available in patients with severe hepatic impairment.

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.

Effects on ability to drive and use machines
Data suggests that nebivolol does not affect psychomotor function. When driving vehicles or operating machines it should be taken into account that dizziness and fatigue may occasionally occur.

ADVERSE REACTIONS

Immune system disorders
Not known: angioneurotic oedema, hypersensitivity

Psychiatric disorders
Uncommon: nightmares, depression,
Not known: Insomnia
Nervous system disorders
Common: headache, dizziness, paraesthesia
Very rare: syncope
Not known: somnolence, vertigo
Eye disorders
Uncommon: impaired vision
Cardiac disorders
Uncommon: bradycardia, heart failure, slowed AV conduction/AV-block
Not known: atrioventricular block (both second and third degree), myocardial infarction, peripheral ischemia/claudication
Vascular disorders
Uncommon: hypotension, (increase of) intermittent claudication
Respiratory, thoracic and mediastinal disorders
Common: dyspnea
Uncommon: bronchospasm
Gastrointestinal disorders
Common: constipation, nausea, diarrhea
Uncommon: dyspepsia, flatulence, vomiting
Skin and subcutaneous tissue disorders
Uncommon: pruritus, rash erythematous
Very rare: psoriasis aggravated
Reproductive system and breast disorders
Uncommon: impotence
General disorders and administration site conditions
Common: tiredness, edema

DRUG INTERACTIONS

CYP2D6 Inhibitors
Drugs that inhibit CYP2D6 can be expected to increase plasma levels of nebivolol. Caution is advised when nebivolol is co-administered with CYP2D6 inhibitors (quinidine, propafenone, fluoxetine, paroxetine, etc.).

Hypotensive Agents
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.

Digitalis Glycosides
Both digitalis glycosides and β-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.

Calcium Channel Blockers
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.

Class I and Class III anti-arrhythmics
Combinations of Class I antiarrythmics and nebivolol is not recommended as the effect on atrio-ventricular conduction time may be potentiated and the negative inotropic effect increased Insulin and oral anti-diabetic drugs.

Insulin and oral anti-diabetic drugs
Insulin and oral anti-diabetic drugs as, although nebivolol does not affect glucose levels, concomitant use may mask symptoms of hypoglycaemia (palpitations, tachycardia).

USE IN SPECIAL POPULATIONS

Pregnancy
US FDA Category C: There are no adequate and well-controlled data in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Nursing mother
Because of the potential for β-blockers to produce serious adverse reactions in nursing infants, especially bradycardia, Nebivolol is not recommended during nursing.

Pediatrics
Safety and effectiveness in pediatric patients have not been established. No data is available for pediatric patients of agesfrom newborn to 18 years old because of incomplete characterization of developmental toxicity and possible adverse effects on long-term fertility.

Elderly
No overall differences in efficacy or in the incidence of adverse events are observed between older and younger patients.

Renal impairment
Dose reduction is recommended (See Dosage & Administration).

Hepatic impairment
Dose reduction is recommended (See Dosage & Administration).

OVER DOSAGE
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.
If overdose occurs, provide general supportive and specific symptomatic treatment. Based on expected pharmacologic actions and recommendations for other β-blockers, consider the following general measures, including stopping Nebivolol, when clinically warranted:
Bradycardia: Administer IV atropine. If the response is inadequate, isoproterenol or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transthoracic or transvenous pacemaker placement may be necessary.
Hypotension: Administer IV fluids and vasopressors. Intravenous glucagon may be useful.
Heart Block (second or third degree): Monitor and treat with isoproterenol infusion. Under some circumstances, transthoracic or transvenous pacemaker placement may be necessary.
Congestive Heart Failure: Initiate therapy with digitalis glycoside and diuretics. In certain cases, consider the use of inotropic and vasodilating agents.
Bronchospasm: Administer bronchodilator therapy such as a short acting inhaled β2-agonist and/or aminophylline.
Hypoglycemia: Administer IV glucose. Repeated doses of IV glucose or possibly glucagon may be required.
Supportive measures should continue until clinical stability is achieved.

PRESENTATION

ByVas 2.5mg
Pack of 14 Tablets.
ByVas 5mg
Pack of 14 Tablets.
ByVas 10mg
Pack of 14 Tablets.

INSTRUCTION
Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 30°C.
For suspected adverse drug reaction, report at
reports@pharmevo.biz

For more information on our products
call PharmAssist helpline 0800-82222
Monday to Friday 9:00 am to 6:00 pm
or email us at : pharmassist@pharmevo.biz

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ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔
تمام دوائیں بچوں کی پہنچ سے دُور رکھیں۔
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Manufactured by:
PharmEvo (Pvt.) Ltd.
Plot # A-29, North Western
Industrial Zone, Port Qasim,
Karachi-75020, Pakistan.
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