Leaflet size as per **(Naxolit Tablet)** WnsFeild Pharmaceuticals

Front

Nabiz™

(NEBIVOLOL)

TABLET

نیبِز

COMPOSITION:

Nabiz Tablet 2.5 mg:
Each tablet contains:
Nebivolol (as HCl) ..... 2.5 mg.

Product Specs.: Innovator

Nabiz Tablet 5 mg:
Each tablet contains:
Nebivolol (as HCl) ..... 5 mg.

Product Specs.: Innovator

Nabiz Tablet 10 mg:
Each tablet contains:
Nebivolol (as HCl) ..... 10 mg.

Product Specs.: Innovator

DESCRIPTION:
Nebivolol is a selective beta blocker agent. Nebivolol is a racemate composed of d-Nebivolol and l-Nebivolol with the stereochemical designations of [SRRR]-nebivolol and [RSSS] nebivolol, respectively.

Clinical Pharmacology:
Nebivolol is a β-adrenergic receptor blocking agent. 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.

Mechanism of action:
The mechanism of action of the antihypertensive response of **Nabiz** 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.

Pharmacokinetics:
Nebivolol is metabolized by a number of routes, including glucuronidation and hydroxylation by CYP2D6. The active isomer (d-nebivolol) has an effective half-life of about 12 hours in CYP2D6 extensive metabolizers (most people), and 19 hours in poor metabolizers and exposure to d-nebivolol is substantially increased in poor metabolizers.

Absorption: 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.

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.

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

INDICATIONS:
1. Hypertension
2. Chronic heart failure (CHF)
a.) Treatment of chronic heart failure in addition to standard therapies in elderly patients of 70 years or older.

DOSAGE AND ADMINISTRATION:
Hypertension: The dose of **Nabiz** 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 at the same time of the day. The blood pressure lowering effect becomes evident after 1-2 weeks of treatment. Occasionally, the optimal effect is reached only after 4 weeks.

Combination with other antihypertensive agents: Beta-blockers can be used alone or concomitantly with other antihypertensive agents.

Chronic heart failure (CHF): The treatment of stable chronic heart failure has to be initiated with a gradual uptitration of dosage until the optimal individual maintenance dose is reached. Patients should have stable chronic heart failure without acute failure during the past six weeks. It is recommended that the treating physician should be experienced in the management of chronic heart failure. For those patients receiving cardiovascular drug therapy including diuretics and/or digoxin and/or ACE inhibitors and/or angiotensin II antagonists, dosing of these drugs should be stabilized during the past two weeks prior to initiation of Nebivolol treatment. The initial uptitration should be done according to the following steps at 1-2 weekly intervals based on patient tolerability: 1.25 mg nebivolol, to be increased to 2.5 mg nebivolol once daily, then to 5 mg once daily and then to 10 mg once daily. The maximum recommended dose is 10 mg nebivolol once daily. Initiation of therapy and every dose increase should be done under the supervision of an experienced physician over a period of at least 2 hours to ensure that the clinical status (especially as regards blood pressure, heart rate, conduction disturbances, signs of worsening of heart failure) remains stable. Occurrence of adverse events may prevent all patients being treated with the maximum recommended dose. If necessary, the dose reached can also be decreased step by step and reintroduced as appropriate. During the titration phase, in case of worsening of the heart failure or intolerance, it is recommended first to reduce the dose of nebivolol, or to stop it immediately if necessary (in case of severe hypotension, worsening of heart failure with acute pulmonary oedema, cardiogenic shock, symptomatic bradycardia or AV block).Treatment of stable chronic heart failure with nebivolol is generally a long-term treatment. The treatment with nebivolol is not recommended to be stopped abruptly since this might lead to a transitory worsening of heart failure. If discontinuation is necessary, the dose should be gradually decreased divided into halves weekly.

Special Populations:
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. Nabiz 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. Nabiz has not been studied in patients with severe hepatic impairment and therefore it is not recommended in that population.

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Elderly:
No dose adjustment is required since up-titration to the maximum tolerated dose is individually adjusted.
Children and adolescents:
Nebivolol is not recommended for use in children and adolescents below 18 years of age due to lack of data on safety and efficacy

CONTRAINDICATIONS:
Nabiz 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.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:
The most common adverse events that led to discontinuation of Nebivolol were headache (0.4%), nausea (0.2%) and bradycardia (0.2%). Other adverse events rarely seen are: Headache, Fatigue, Dizziness, Diarrhea, Nausea, Insomnia, Chest pain, Bradycardia, Dyspnea, Rash, Peripheral edema.
Abrupt cessation of therapy: Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in patients with coronary artery disease following the abrupt discontinuation of therapy with β-blockers. As with other β-blockers, when discontinuation of Nebivolol is planned, patients should be carefully observed and advised to minimize physical activity. Nebivolol should be tapered over 1 to 2 weeks when possible. If the angina worsens or acute coronary insufficiency develops, it is recommended that Nebivolol be promptly reinstituted, at least temporarily.
Cardiac failure: In patients who have compensated congestive heart failure, Nebivolol should be administered cautiously. If heart failure worsens, discontinuation of Nebivolol should be considered.
Angina and acute myocardial infarction: Nebivolol 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: If Nebivolol is to be continued perioperatively, patients should be closely monitored 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. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be advised about these possibilities and nebivolol should be used with caution.
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. Caution should be exercised in these patients.
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, caution should be used in patients treated concomitantly with these agents and ECG and blood pressure should be monitored.
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. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reactions. In patients with known or suspected pheochromocytoma, an alpha-blocker should be initiated prior to the use of any β-blocker.

DRUG INTERACTIONS:
Nebivolol should be used with care when myocardial depressants or inhibitors of AV conduction, such as certain calcium antagonists, or antiarrhythmic agents, are used concurrently. Both digitalis glycosides and β-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia. Nebivolol should not be combined with other β-blockers. In patients who are receiving Nebivolol and clonidine, Nebivolol should be discontinued for several days before the gradual tapering of clonidine.
Laboratory abnormalities: In controlled monotherapy trials of hypertensive patients, Nebivolol was associated with an increase in BUN, uric acid, triglycerides and a decrease in HDL cholesterol and platelet count.
CYP2D6 inhibitors: Use caution when Nebivolol is co- administered with CYP2D6 inhibitors (quinidine, propafenone, fluoxetine, paroxetine, etc.)

PREGNANCY & LACTATION:
Pregnancy Category C: No studies of nebivolol were conducted in pregnant women. Nebivolol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nursing mothers: Nebivolol is not recommended during nursing.

OVERDOSE:
The most common signs and symptoms associated with Nebivolol overdosage are bradycardia and hypotension. Other important adverse events reported with Nebivolol overdose include cardiac failure, dizziness, hypoglycemia, fatigue and vomiting. Other adverse events associated with β-blocker overdose include bronchospasm and heart block. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to enhance nebivolol clearance. If overdose occurs, Nebivolol should be stopped and general supportive and specific symptomatic treatment should be provided.

INSTRUCTIONS:
- Store below 30°C.
- Protect from heat, sunlight & moisture.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:

Nabiz Tablet 2.5 mg	:	Pack of 2 x 7 tablets.
Nabiz Tablet 5 mg	:	Pack of 2 x 7 tablets.
Nabiz Tablet 10 mg	:	Pack of 2 x 7 tablets.

ہدایات:
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف ڈاکٹر کے نسخہ پر فروخت کریں۔

Manufactured by:
WnsFeild Pharmaceuticals.
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FOR FURTHER INFORMATION PLEASE CONTACT:

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