



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NEBIVOLOL TABLETS safely and effectively. See full prescribing information for NEBIVOLOL TABLETS.

NEBIVOLOL tablets, for oral use
Initial U.S. Approval: 2007

Warnings and Precautions, Hypoglycemia (5.5) 6/2023

INDICATIONS AND USAGE
Nebivolol tablet is a beta-adrenergic blocking agent 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. (1.1)

DOSAGE AND ADMINISTRATION
Can be taken with and without food. Individualize to the needs of the patient and monitor during up-titration. (2)

CONTRAINDICATIONS
Severe bradycardia (4)
Heart block greater than first degree (4)
Patients with cardiogenic shock (4)
Decompensated cardiac failure (4)

- Sick sinus syndrome (unless a permanent pacemaker is in place) (4)
- Patients with severe hepatic impairment (Child-Pugh >B) (4)
- Hypersensitive to any component of this product (4)

WARNINGS AND PRECAUTIONS
Acute exacerbation of coronary artery disease upon cessation of therapy: Do not abruptly discontinue. (5.1)
Diabetes: May mask symptoms of hypoglycemia and alter glucose levels; monitor (5.5)

ADVERSE REACTIONS
Most common adverse reactions (6.7):
Headache, fatigue

To report SUSPECTED ADVERSE REACTIONS, Contact Hetero Labs Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
CYP2D6 enzyme inhibitors may increase nebivolol levels. (7.1)
Reserpine or clonidine may produce excessive reduction of sympathetic activity. (7.2)
Both digitalis glycosides and beta-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia. (7.3)
Verapamil- or diltiazem-type calcium channel blockers may cause excessive reductions in heart rate, blood pressure, and cardiac contractility. (7.4)

USE IN SPECIFIC POPULATIONS
Lactation: Breastfeeding is not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling. Revised: 11/2023

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FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

1.1 Hypertension

Nebivolol tablets are indicated for the treatment of hypertension, to lower blood pressure [see Clinical Studies (14.1)]. Nebivolol tablets may be used alone or in combination with other antihypertensive agents [see Drug Interactions (7)].

Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been shown in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes, including the class to which this drug principally belongs. There are no controlled trials demonstrating risk reduction with nebivolol tablets.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

2. DOSAGE AND ADMINISTRATION

2.1 Hypertension

The dose of nebivolol tablets 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 (CrCl less than 30 mL/min) the recommended initial dose is 2.5 mg once daily; titrate up slowly if needed. Nebivolol tablets have not been studied in patients receiving dialysis [see Clinical Pharmacology (12.4)].

Hepatic Impairment

In patients with moderate hepatic impairment, the recommended initial dose is 2.5 mg once daily; titrate up slowly if needed. Nebivolol tablets have not been studied in patients with severe hepatic impairment and therefore it is not recommended in that population [see Clinical Pharmacology (12.4)].

2.2 Subpopulations

Geriatric Patients

It is not necessary to adjust the dose in the elderly [see use in Specific Populations (8.5)].

CYP2D6 Polymorphism

No dose adjustments are necessary for patients who are CYP2D6 poor metabolizers. The clinical effect and safety profile observed in poor metabolizers were similar to those of extensive metabolizers [see Clinical Pharmacology (12.3)].

3. DOSAGE FORMS AND STRENGTHS

Nebivolol is available as tablets for oral administration containing nebivolol hydrochloride equivalent to 2.5, 5, 10, and 20 mg of nebivolol.

Nebivolol tablets, 2.5 mg are white to off-white, triangular biconvex tablets debossed with 'J' on one side and '8' on other side.

Nebivolol tablets, 5 mg are light orange, triangular biconvex tablets debossed with 'J' on one side and '9' on other side.

Nebivolol tablets, 10 mg are light peach color, triangular shaped biconvex tablets debossed with 'J' on one side and '10' on other side.

Nebivolol tablets, 20 mg are white to off-white, triangular biconvex tablets debossed with 'J' on one side and '11' on other side.

4. CONTRAINDICATIONS

Nebivolol tablets are 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.

5. WARNINGS AND PRECAUTIONS

5.1 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 have been reported in patients with coronary artery disease following the abrupt discontinuation of therapy with beta-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 beta-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.

5.2 Angina and Acute Myocardial Infarction

Nebivolol was not studied in patients with angina pectoris or who had a recent MI.

5.3 Bronchospastic Diseases

In general, patients with bronchospastic diseases should not receive beta-blockers.

5.4 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 beta-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 beta-blocking effects of nebivolol can be reversed by beta-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 beta-blockers.

5.5 Hypoglycemia

Beta-blockers may prevent early warning signs of hypoglycemia, such as tachycardia, and increase the risk for severe or prolonged hypoglycemia at anytime during treatment, especially in patients with diabetes mellitus or children and patients who are fasting (i.e., surgery, not eating regularly, or are vomiting). If severe hypoglycemia occurs, patients should be instructed to seek emergency treatment.

5.6 Thyrotoxicosis

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

5.7 Peripheral Vascular Disease

beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease.

5.8 Non-dihydropyridine Calcium Channel Blockers

Because of significant negative inotropic and chronotropic effects in patients treated with beta-blockers and calcium channel blockers of the verapamil and diltiazem type, monitor the ECG and blood pressure in patients treated concomitantly with these agents.

5.9 Use with CYP2D6 Inhibitors

Nebivolol exposure increases with inhibition of CYP2D6 [see Drug Interactions (7)]. The dose of nebivolol may need to be reduced.

5.10 Impaired Renal Function

Renal clearance of nebivolol is decreased in patients with severe renal impairment. Nebivolol has not been studied in patients receiving dialysis [see Clinical Pharmacology (12.4) and Dosage and Administration (2.1)].

5.11 Impaired Hepatic Function

Metabolism of nebivolol is decreased in patients with moderate hepatic impairment. Nebivolol has not been studied in patients with severe hepatic impairment [see Clinical Pharmacology (12.4) and Dosage and Administration (2.1)].

5.12 Risk of Anaphylactic Reactions

While taking beta-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.

5.13 Pheochromocytoma

In patients with known or suspected pheochromocytoma, initiate an alpha-blocker prior to the use of any beta-blocker.

6. ADVERSE REACTIONS

6.1 Clinical Studies Experience

Nebivolol has been evaluated for safety in patients with hypertension and in patients with heart failure. The observed adverse reaction profile was consistent with the pharmacology of the drug and the health status of the patients in the clinical trials. Adverse reactions reported for each of these patient populations are provided below. Excluded are adverse reactions considered too general to be informative and those not reasonably associated with the use of the drug because they were associated with the condition being treated or are very common in the treated population.

The data described below reflect worldwide clinical trial exposure to nebivolol in 6,545 patients, including 5,038 patients treated for hypertension and the remaining 1,507 subjects treated for other cardiovascular diseases. Doses ranged from 0.5 mg to 40 mg. Patients received nebivolol for up to 24 months, with over 1,900 patients treated for at least 6 months, and approximately 1,300 patients for more than one year.

HYPERTENSION: In placebo-controlled clinical trials comparing nebivolol with placebo, discontinuation of therapy due to adverse reactions was reported in 2.8% of patients treated with nebivolol and 2.2% of patients given placebo. The most common adverse reactions that led to discontinuation of nebivolol were headache (0.4%), nausea (0.2%) and bradycardia (0.2%).

Table 1 lists treatment-emergent adverse reactions that were reported in three 12-week, placebo-controlled monotherapy trials involving 1,597 hypertensive patients treated with either 5 mg, 10 mg, or 20 to 40 mg of nebivolol and 205 patients given placebo and for which the rate of occurrence was at least 1% of patients treated with nebivolol and greater than the rate for those treated with placebo in at least one dose group.

Table 1. Treatment-Emergent Adverse Reactions with an Incidence (over 6 weeks) ≥ 1% in Nebivolol-Treated Patients and at a Higher Frequency than Placebo-Treated Patients

System Organ Class – Preferred Term	Placebo (n = 205) (%)	Nebivolol 5 mg (n = 459) (%)	Nebivolol 10 mg (n = 461) (%)	Nebivolol 20 to 40 mg (n = 677) (%)
Cardiac Disorders				
Bradycardia	0	0	0	1
Gastrointestinal Disorders				
Diarrhea	2	2	2	3
Nausea	0	1	3	2
General Disorders				
Fatigue	1	2	2	5
Chest pain	0	0	1	1
Peripheral edema	0	1	1	1
Nervous System Disorders				
Headache	6	9	6	7
Dizziness	2	2	3	4
Psychiatric Disorders				
Insomnia	0	1	1	1
Respiratory Disorders				
Dyspnea	0	0	1	1
Skin and subcutaneous Tissue Disorders				
Rash	0	0	1	1

Listed below are other reported adverse reactions with an incidence of at least 1% in the more than 4,300 patients treated with nebivolol in controlled or open-label trials except for those already appearing in Table 1, terms too general to be informative, minor symptoms, or adverse reactions unlikely to be attributable to drug because they are common in the population. These adverse reactions were in most cases observed at a similar frequency in placebo-treated patients in the controlled studies.

Body as a Whole: asthenia.

Gastrointestinal System Disorders: abdominal pain

Metabolic and Nutritional Disorders: hypercholesterolemia

Nervous System Disorders: paraesthesia

6.2 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.

6.3 Postmarketing Experience

The following adverse reactions have been identified from spontaneous reports of nebivolol received worldwide and have not been listed elsewhere. These adverse reactions have been chosen for inclusion due to a combination of seriousness, frequency of reporting or potential causal connection to nebivolol. Adverse reactions common in the population have generally been omitted. Because these adverse reactions were reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency or establish a causal relationship to nebivolol exposure: abnormal hepatic function (including increased AST, ALT and bilirubin), acute pulmonary edema, acute renal failure, atrioventricular block (both second and third degree), bronchospasm, erectile dysfunction, hypersensitivity (including urticaria, allergic vasculitis and rare reports of anaphylaxis), hypotension, myocardial infarction, pruritus, psoriasis, Raynaud's phenomenon, peripheral ischemia/claudication, somnolence, syncope, thrombocytopenia, various rashes and skin disorders, vertigo, and vomiting.

7. DRUG INTERACTIONS

7.1 CYP2D6 Inhibitors

Use caution when nebivolol is co-administered with CYP2D6 inhibitors (quinidine, propafenone, fluoxetine, paroxetine, etc.) [see Clinical Pharmacology (12.5)].

7.2 Hypotensive Agents

Do not use nebivolol with other beta-blockers. Closely monitor patients receiving catecholamine-depleting drugs, such as reserpine or guanethidine, because the added beta-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.

7.3 Digitalis Glycosides

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

7.4 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.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary 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 [see Clinical Considerations]. Oral administration of nebivolol to pregnant rats during organogenesis resulted in embryofetal and perinatal lethality at doses approximately equivalent to the maximum recommended human dose (MRHD).

PATIENT INFORMATION

Nebivolol Tablets (ne BIV oh lol)

Read the Patient Information that comes with nebivolol tablets before you start taking them and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about nebivolol tablets, ask your doctor or pharmacist.

WHAT ARE NEBIVOLOL TABLETS?

Nebivolol tablet is a kind of prescription medicine called a "beta-blocker". Nebivolol tablet treats:

- High blood pressure (hypertension)
- Nebivolol tablets can lower blood pressure when used by itself and with other medicines.
- Nebivolol tablets are not approved for children less than 18 years of age.

WHO SHOULD NOT TAKE NEBIVOLOL TABLETS?

Do not take nebivolol tablets if you:

- Have heart failure and are in the ICU or need medicines to keep up your blood circulation
- Have a slow heartbeat or your heart skips beats (irregular heartbeat)
- Have severe liver damage
- Are allergic to any ingredient in nebivolol tablets. The active ingredient is nebivolol. See the end of this leaflet for a list of ingredients.

WHAT SHOULD I TELL MY DOCTOR BEFORE TAKING NEBIVOLOL TABLETS?

Tell your doctor about all of your medical problems, including if you:

- Have asthma or other lung problems (such as bronchitis or emphysema)
- Have problems with blood flow in your feet and legs (peripheral vascular disease). Nebivolol tablets can make symptoms of blood flow problems worse.
- Have diabetes and take medicine to control blood sugar
- Have thyroid problems
- Have liver or kidney problems
- Had allergic reactions to medications or have allergies
- Have a condition called pheochromocytoma
- Are pregnant or trying to become pregnant. It is not known if nebivolol tablets are safe for your unborn baby. Talk with your doctor about the best way to treat high blood pressure while you are pregnant.
- Are breastfeeding. It is not known if nebivolol passes into your breast milk. You should not breastfeed while using nebivolol tablets.
- Are scheduled for surgery and will be given anesthetic agents

Tell your doctor about all the medicines you take. Include prescription and non-prescription medicines, vitamins, and herbal products. Nebivolol tablets and certain other medicines can affect each other and cause serious side effects.

Keep a list of all the medicines you take. Show this list to your doctor and pharmacist before you start a new medicine.

HOW SHOULD I TAKE NEBIVOLOL TABLETS?

- Do not suddenly stop taking nebivolol tablets. You could have chest pain or a heart attack. If your doctor decides to stop nebivolol tablets, your doctor may slowly lower your dose over time before stopping it completely.
- Take nebivolol tablets every day exactly as your doctor tells you. Your doctor will tell you how much nebivolol tablets to take and how often. Your doctor may start with a low dose and raise it over time. Do not stop taking nebivolol tablets or change your dose without talking with your doctor.
- Take nebivolol tablets with or without food.
- If you miss a dose, take your dose as soon as you remember, unless it is close to the time to take your next dose. Do not take 2 doses at the same time. Take your next dose at the usual time.

Dimensions	250 x 480 mm (Folded: 32 x 32 mm)
Customer/Country	Camber / USA
Spec	Bible Paper 40 GSM
Pantone Colours	Black
Version No.	00



