# Nobu Tablets*

# نوبو ٹیبلٹس

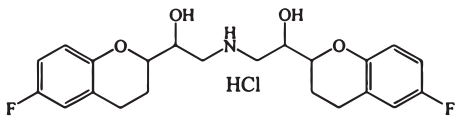
**COMPOSITION**

Each tablet contains:

Nebivolol HCl eq. To Nebivolol*.....2.5 & 5 mg, respectively.

**DESCRIPTION**

The chemical name of nebivolol 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 hydrochloride is a white to almost white powder that is soluble in methanol, dimethylsulfoxide, and N,N-dimethylformamide, sparingly soluble in ethanol, propylene glycol, and polyethylene glycol, and very slightly soluble in hexane, dichloromethane, and methylbenzene. The molecular formula of Nebivolol HCl is ($C_{22}H_{25}F_2N_8$•HCl) with the following structural formula:




**CLINICAL PHARMACOLOGY**

Nebivolol, a racemic mixture of SRRR and RSSS, 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. At clinically relevant doses, nebivolol does not demonstrate α1 - adrenergic receptor blockade activity. Various metabolites, including glucuronides, contribute to β-blocking activity.

**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.

**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 (EMs) and 19 hours in poor metabolizers (PMs) and exposure to d-nebivolol is substantially increased in PMs. This has less importance than usual, however, because the metabolites, including the hydroxyl metabolite and glucuronides (the predominant circulating metabolites), contribute to β-blocking activity. Plasma levels of d-nebivolol increase in proportion to dose in EMs and PMs for doses up to 20 mg. Exposure to l-nebivolol is higher than to d-nebivolol but l-nebivolol contributes little to the drug's activity as beta receptor affinity of d-nebivolol is >1000-fold higher than l-nebivolol. For the same dose, PMs attain a 5-fold higher Cmax and 10-fold higher AUC of d-nebivolol than do EMs. d-nebivolol accumulates about 1.5-fold with repeated once-daily dosing in EMs.

***Absorption:*** Nebivolol is rapidly absorbed following oral administration. 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. NOBU 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 nebivolol, 38% of the dose is recovered in urine and 44% in feces for EMs and 67% in urine and 13% in feces for PMs. 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 increases 3-fold, exposure (AUC) increases 10-fold, and the apparent clearance decreases by 86% in patients with moderate hepatic impairment (Child-Pugh Class B). The starting dose should be reduced in patients with moderate hepatic impairment. Nebivolol is contraindicated for patients with severe hepatic impairment 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), and it is reduced negligibly in patients with moderate (CLcr 30 to 50 mL/min), but clearance is reduced by 53% in patients with severe renal impairment (CLcr <30 mL/min). The dose of nebivolol should be adjusted in patients with severe renal impairment.

**INDICATIONS AND USAGE**

**Hypertension:** NOBU (Nebivolol) is indicated for the treatment of essential hypertension, to lower blood pressure. NOBU may be used alone or in combination with other antihypertensive agents.

**CONTRAINDICATIONS**

Nebivolol (NOBU) 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.

**ADVERSE REACTIONS**

**Common adverse reactions:** The common adverse reactions with nebivolol are headache, bradycardia, dizziness, paresthesia, dyspnea, constipation, nausea, diarrhea, fatigue, chest pain, peripheral edema, insomnia, dyspnea and rash. **Laboratory Abnormalities:** Nebivolol is associated with an increase in BUN, uric acid, triglycerides and a decrease in HDL cholesterol and platelet count.

**DRUG INTERACTIONS**

**CYP2D6 Inhibitors:** Use caution when nebivolol (NOBU) is co-administered with CYP2D6 inhibitors (quinidine, propafenone, fluoxetine, paroxetine, etc.). **Hypotensive Agents:** Do not use nebivolol (NOBU) with other β-blockers. Closely monitor patients receiving catecholamine-depleting drugs, such as reserpine or guanethidine, because the added β-blocking action of nebivolol (NOBU) may produce excessive reduction of sympathetic activity. In patients who are receiving

nebivolol (NOBU) and clonidine, discontinue nebivolol (NOBU) 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 (NOBU) can exacerbate the effects of myocardial depressants or inhibitors of AV conduction, such as certain calcium antagonists (particularly of the phenylalkylamine [verapamil] and benzodiazepine [diltiazem] classes), or antiarrhythmic agents, such as disopyramide.

## USE IN SPECIFIC POPULATION

**Pregnancy:** Pregnancy Category C: Nebivolol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** Because of the potential for β-blockers to produce serious adverse reactions in nursing infants, especially bradycardia, nebivolol (NOBU) is not recommended during nursing. **Pediatric Use:** Safety and effectiveness of nebivolol in pediatric patients have not been established. **Geriatric Use:** No overall differences in efficacy or in the incidence of adverse events are observed between older and younger patients. **Heart Failure:** If heart failure worsens consider discontinuation of nebivolol (NOBU).

## WARNINGS AND PRECAUTIONS

**Abrupt Cessation of Therapy** Do not abruptly discontinue nebivolol (NOBU) 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 β-blockers. Caution patients without overt coronary artery disease against interruption or abrupt discontinuation of therapy. Taper nebivolol (NOBU) over 1 to 2 weeks when possible. If the angina worsens or acute coronary insufficiency develops, restart nebivolol (NOBU) promptly, at least temporarily. **Angina and Acute Myocardial Infarction:** Nebivolol (NOBU) is not studied in patients with angina pectoris or who had a recent MI. **Bronchospastic Diseases:** 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 (NOBU) is to be continued perioperatively, monitor patients closely when anesthetic agents which depress myocardial function 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 (NOBU) can be reversed by β-agonists. 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 the ECG and blood pressure in patients treated concomitantly with these agents. **Use with CYP2D6 Inhibitors:** Nebivolol exposure increases with inhibition of CYP2D6. The dose of nebivolol (NOBU) may need to be reduced. **Impaired Renal Function:** Renal clearance of nebivolol is decreased in patients with severe renal impairment. Nebivolol (NOBU) has not been studied in patients receiving dialysis. **Impaired Hepatic Function:** Metabolism of nebivolol is decreased in patients with moderate hepatic impairment. Nebivolol (NOBU) has not been studied 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 an α-blocker prior to the use of any β-blocker.

## DOSAGE AND ADMINISTRATION

**Hypertension:** The dose of nebivolol (NOBU) 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. Nebivolol 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. Nebivolol has not been studied in patients with severe hepatic impairment and therefore it is not recommended in that population.

## OVERDOSAGE

The most common signs and symptoms associated with nebivolol overdosage are bradycardia and hypotension. Others 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. 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 β 2 -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. The half-life of low doses of nebivolol is 12-19 hours.

**STORAGE/PRECAUTIONS:** Store in a cool, dry and dark place below 25 °C. Keep all medicines out of the reach of children. To be used on the prescription of Registered Medical Practitioners.

**PRESENTATION:** NOBU Tablets 2.5 & 5 mg are available in packing containing 10 tablets, respectively.

*Scotmann Specs.

خوراک: ڈاکٹر کی ہدایت کے مطابق۔ احتیاط: روشنی، نمی اور گرمی سے بچائیں۔
25 ڈگری سینٹی گریڈ سے کم درجہ حرارت پر محفوظ کریں۔
تمام ادویات بچوں کی پہنچ سے دور رکھیں۔ مستند ڈاکٹر کے نسخہ پر استعمال کریں۔

Complete Medical Information available only for doctors on request.

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