Nibovo

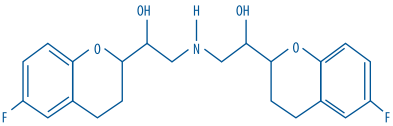
(NEBIVOLOL)

نيبوو

2.5mg & 5mg Tablets

DESCRIPTION

Nebivolol is chemically described (1RS, 1'RS)-1, 1-[(2RS, 2'RS) -bis (6-fluro-3,4-dihydro-2H-1 -benzopyran-2-yl)]- 2,2'-imi8nodiethanol hydrochloride. Its molecular formula is C22H25F2NO4 and its structural formula is:



QUANTITATIVE AND QUALITATIVE COMPOSITION

NIBOVO (Nebivolol) Tablets are available for oral administration as:

NIBOVO Tablets 2.5mg
Each tablet contains:
Nebivolol HCl equivalent to Nebivolol… 2.5mg

NIBOVO Tablets 5mg
Each tablet contains:
Nebivolol HCl equivalent to Nebivolol… 5mg

CLINICAL PHARMACOLOGY

Mechanism of action

The mechanism of action of the antihypertensive response of NIBOVO has not been definitively established. Possible factors that may be involved include: decreased heart rate, decreased myocardial contractility, diminution of tonic sympathetic outflow to the periphery from cerebral vasomotor centers, suppression of rennin activity and vasodilation and decreased peripheral vascular resistance.

Pharmacokinetics

Absorption of NIBOVO is similar to an oral solution. 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. NIBOVO may be administered without regard to meals. The in vitro human plasma protein binding of Nebivolol is approximately 98%, mostly to albumin, and is independent of Nebivolol concentrations. Nebivolol is predominantly metabolized via direct glucuronidation of parent and to a lesser extent via N-dealkylation and oxidation via cytochrome P450 2D6. Its stereo specific metabolites contribute to the pharmacologic activity. 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.

Special Populations

Renal Impairment

The apparent clearance of nebivolol is unchanged following a single 5mg dose of Nebivolol in patients with mild renal impairment (CLcr50 to 80L/min).However it is reduced negligibly in patients with severe renal impairment (CLCR<30ml/min). But clearance was 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.

Hepatic Impairment

Nebivolol peak plasma concentration increased 3 fold, exposure (AUC) increased 10-fold, and the apparent clearance decreased by 86% in patients with moderate hepatic impairment (Child-Pugh Class B). The starting dose should be reduced in patients with moderate hepatic impairment.

THERAPEUTIC INDICATIONS

NIBOVO (Nebivolol) is indicated for the treatment of the following:

Hypertension

Treatment of essential hypertension

NIBOVO (Nebivolol) maybe used alone or in combination with other antihypertensive agents.

DOSAGE AND ADMINISTRATION

Hypertension

Adults

The dose is one tablet (5mg) daily, at the same time of the day. Tablets may be taken with or without meals .The initial titration should be done at 1-2weekly intervals based on patient's tolerability. The maximum recommended dose is 10mg nebivolol once daily. The blood pressure lowering effect becomes evident after1-2 weeks of treatment. Occasionally, the optimal effect is reached after 4 weeks. 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 edema , cardiogenic shock, symptomatic bradycardia or AV block).

Patients with renal impairment

In patients with moderate hepatic impairment, the recommended initial dose is 2.5mg once daily. Upward titration should be performed cautiously if needed.

Elderly

IN patients with over 65 years the recommended dose is 2.5mg daily. If needed, the daily dose may be increased to 5mg.

Chronic heart failure

The treatment of stable chronic heart failure is to be initiated with a gradual up titration 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 stabilize during the past two weeks prior to initiation of nebivolol treatment.

ADVERSE REACTIONS

The following adverse reactions occurred:

Hypertension

Common: Headache, dizziness, paresthesia, dyspnea, constipation, nausea, diarrhea, tiredness and edema.
Uncommon: Nightmares, depression, impaired vision, bradycardia, heart failure, slowed AV conduction/AV-block, hypotension, (increase of) intermittent claudication, bronchospasm, dyspepsia, flatulence, vomiting, pruritus, rash, erythematous and impotence.
Rare: Syncope and psoriasis aggravated.

Chronic Heart Failure

The most commonly reported adverse reactions are bradycardia and dizziness. The other adverse reactions that occurred are aggravation of cardiac failure, postural hypotension, drug intolerance, first degree atrio-ventricular block and edema of the lower limb occurred.

CONTRAINDICATIONS

Nebivolol is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the component of product.
- Severe hepatic impairment (Child Pugh >B)
- Acute heart failure, cardiogenic shock or episodes of heart failure decomposition requiring I.V. inotropic therapy.
- Sick sinus syndrome,including sino-atrial block.
- Second and third degree heart block (without a pacemaker).
- History of bronchospasm and bronchial asthma.
- Untreated phaeochromocytoma.
- Metabolic acidosis.
- Bradycardia (heart rate <60bpm prior to start of therapy).
- Hypotension (systolic blood pressure <90 mmHg).
- Severe peripheral circulatory disturbances.

PRECAUTIONS

Anesthesia

Continuation of beta blockade reduces the risk of arrhythmias during induction and intubation. If beta blockade is interrupted in preparation for surgery, the beta- adrenergic antagonist should be discontinued at least 24 hours before hand.

Caution should be observed with certain anesthetics that cause myocardial depression. The patient can be protected against vagal reactions by intravenous administration of atropine.

Cardiac Failure

In patients who have compensated congestive heart failure, nebivolol should be administrated cautiously. if heart failure worsens, discontinuation of nebivolol should be considered.

Metabolic /Endocrinological

Care should be taken in diabetic patients however nebivolol may mask certain symptoms of hypoglycemia (tachycardia, palpitations). Beta adrenergic blocking agents may mask tachycardia symptoms in hyperthyroidism. Abrupt withdrawal may intensify symptoms.

Abrupt Cessation of Therapy

The treatment 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. If the angina worsens or acute coronary insufficiency develops, it is recommended that nebivolol be promptly reinstituted, at least temporarily.

Peripheral Vascular Disease

B-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Cautions should be exercised in these patients.

Renal Impairment

Nebivolol should be used with caution in patients receiving dialysis.

Geriatric Patients

In patients with 75 years ,caution must be exercised and these patients monitored closely.

Others

- Patients with a history of psoriasis should be taking β-adrenergic Antagonist only after carefull consideration β-adrenergic antagonist may increase the sensitivity to allergens and the severity of anaphylactic reactions.
- Patients with rare hereditary problems of galactose intolerance, the lapp-lactase deficiency or glucose–galactose malabsorption should not take this medical product.

Pregnancy

Nebivolol should be used during pregnancy (category C) only if the potential benefit justifies the potential risk to the fetus. If treatment with nebivolol is considered necessary, the uteroplacental blood flow and the fetal growth should be monitored. In case of harmful effects on pregnancy or the fetus alternative treatment should be considered. The newborn infant must be closely monitored. Symptoms of hypoglycemia and bradycardia are generally to be expected with the first 3 days.

Nursing Mothers

It is not known whether this drug is excreted in human milk or not. Because of the potential for β-blockers to produce serious adverse reactions in nursing infants, especially bradycardia. Nebivolol is not recommended during nursing.

Drug Interactions

- Nebivolol should be used with care when 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 are used concurrently.
- Both digitalis glycosides and ß-blockers slow antrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.
- Patients receiving catecholamine-depleting drugs such as reserpine or guanethidine should be closely monitored.
- In patients who are receiving nebivolol and clonidine, nebivolol should be discontinued for several days before the gradual tapering of clonidine.

CYP2D6 *inhibitors:* Caution should be used when nebivolol is co administrated with CYP2D6 inhibitors (quinidine, propafenone, fluoxetine, paroxetine etc.)

Cimetidine: Cimetidine causes a 23% increase in the plasma levels of d-nebivolol.

Slidenafil: The co-administration of nebivolol and slidenafil decreased AUC and Cmax of slidenafil by 21% and 23% respectively. The effect on the Cmax and AUC for d-nebivolol was also small (<20%).

OVERDOSE

The most common signs and symptoms associated with nebivolol overdosage are bardycardia and hypotension. Other important adverse events reported with nebivolol overdose include cardiac failure, dizziness, hypoglycemia, fatigue and vomiting. Other adverse events associated with ß-blocker overdose include bronchospasm and heart block. If overdose occurs, Nebivolol should be stopped and general supportive and specific symptomatic treatment should be provided.

HOW SUPPLIED

NIBOVO (Nebivolol) Tablets 2.5mg are available in blister pack of 10's.
NIBOVO (Nebivolol) Tablets 5mg are available in blister pack of 10's.

STORAGE

Store at 25°C (Excursions permitted between 15° C-30° C)
Protect from sunlight and moisture.

Keep out of reach of children.
To be sold on prescription of a registered medical practitioner only.
Please read the contents carefully before use.
This package insert is continually updated from time to time.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

احتیاط وہدایات: دھوپ، گرمی اور نمی سے محفوظ رکھیں۔

دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

صرف رجسٹرڈ ڈاکٹر کے نسخہ کے مطابق فروخت کریں۔

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Marketed by:

SCILIFE

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