Nebilol

2.5mg
5mg
10mg

(Nebivolol Hydrochloride)

Tablets

نیبیلول

۲.۵ ملی گرام
۵ ملی گرام
۱۰ ملی گرام ٹیبلٹس

QUALITATIVE AND QUANTITATIVE COMPOSITION

NEBILOL 2.5mg Tablets: Each tablet contains:
Nebivolol HCl equivalent to Nebivolol 2.5mg
Innovator's Specs.

NEBILOL 5mg Tablets: Each tablet contains:
Nebivolol HCl equivalent to Nebivolol 5mg
Innovator's Specs.

NEBILOL 10mg Tablets: Each tablet contains:
Nebivolol HCl equivalent to Nebivolol 10mg
Innovator's Specs.

DESCRIPTION:

Nebivolol is a racemate composed of d-Nebivolol and l-Nebivolol with the stereochemical designations of [SRRR]-Nebivolol and [RSSS]¬Nebivolol, respectively. Nebilol as tablets for oral administration contains Nebivolol hydrochloride equivalent to 2.5, 5, 10, and 20 mg of Nebivolol base.

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. 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 (most people), and 19 hours in poor metabolizers and exposure to d-Nebivolol is substantially increased in poor metabolizers. 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 20mg. Exposure to l- Nebivolol is higher than to d-Nebivolol but l-Nebivolol contributes little to the drug's activity as d-Nebivolol's beta receptor affinity 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:** 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 pharmaco-logic activity. **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 AND USAGE:

Nebivolol 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. **Hypertension:** Treatment of essential hypertension. **Chronic heart failure (CHF):** Treatment of stable mild and moderate chronic heart failure in addition to standard therapies in elderly patients 70 years old or above. NEBILOL(Nebivolol) may be used alone or in combination with other anti-hypertensive agents.

CONTRAINDICATIONS:

• Hypersensitivity to the active substance or to any of the excipients. • Liver insufficiency or liver function impairment. • Acute heart failure, cardiogenic shock or episodes of heart failure decompensation requiring I.V. inotropic therapy. In addition, as with other beta-blocking agents, Nebivolol is contra-indicated in: • Sick sinus syndrome, including sino-atrial block. • Second and third degree heart block (without a pacemaker). • History of bronchospasm and bronchial asthma. • Untreated pheochromocytoma.
• Metabolic acidosis. • Bradycardia (heart rate < 60bpm prior to start of therapy). • Hypotension (systolic blood pressure <90mmHg). • Severe peripheral circulatory disturbances.

INTERACTIONS: CYP2D6 Inhibitors: Use caution 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.

USE IN SPECIFIC POPULATION:

Pregnancy: Category C: Nebivolol has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn. In general, beta-blockers reduce placental profusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse effects (e.g. hypoglycaemia and bradycardia) may occur in the foetus and newborn infant. If treatment with beta-adrenoreceptor blockers is necessary, beta1-selective adrenoreceptor blockers are preferable. Nebivolol should not be used during pregnancy unless clearly necessary. If treatment with Nebivolol is considered necessary, the uteroplacental blood flow and foetal growth should be monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected in the first 3 days. **Lactation:** It is not known whether this drug is excreted into human milk. Therefore breast feeding in not recommended during administration of Nebivolol.
Pediatric Use: Nebivolol is not recommended for use in children and adolescents under the age of 18 years due to a lack of data on safety and efficacy. **Elderly patient:** In patients over 65 years, the recommended starting dose is 2.5mg daily. If needed, the daily dose may be increased to 5mg. However, in view of the limited experience in patients above 75 years, caution must be exercised and these patients monitored closely. **Renal patient:** Nebivolol has not been studied in patients receiving dialysis. No dose adjustment is required in mild to moderate renal insufficiency since up-titration to the maximum tolerated dose is individually adjusted. There is no experience in patients with severe renal insufficiency (serum creatinine ≥ 250µmol/L). Therefore, the use of Nebivolol in these patients is not recommended.

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 have been reported in patients with coronary artery disease following the abrupt discontinuation of therapy with β-blockers.
Angina and Acute Myocardial Infarction: 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:** Because beta-blocker withdrawal has been associated with an increased risk of MI and chest pain, patients already on betablockers 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 has been reported with β-blockers. **Diabetes and Hypoglycemia:** β-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia.
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 may need to be reduced. **Impaired Renal Function:** Renal clearance of Nebivolol is decreased in patients with severe renal impairment. Nebivolol has not been studied in patients receiving dialysis. **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. **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.

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 atrioventriular block and edema of the lower limb occurred. **Side effects:** Depression, oedema.

DOSAGE AND ADMINISTRATION:

Essential hypertension: Nebilol tablets may be taken with or without food, as monotherapy or in combination with other agents. **Adult:** 5 mg daily. **Elderly:** Initially 2.5 mg daily, then increased if necessary to 5 mg daily. 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. The blood pressure lowering effect may take up to 1-2 weeks of treatment to become evident. Occasionally, the optimal effect is only reached only after 4 weeks. Beta-blockers can be used alone or concomitantly with other antihypertensive agents. An additional antihypertensive effect has been observed when Nebivolol 5mg Tablets are combined with hydrochlorothiazide 12.5mg-25mg. **Hypertension in patient with renal impairment: Adult:** Initially 2.5 mg once daily, then increased if necessary to 5 mg once daily. 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. **Adjunct in stable mild to moderate heart failure: Adult 70 years and over:** Initially 1.25 mg once daily for 1–2 weeks, then increased if tolerated to 2.5 mg once daily for 1–2 weeks, then increased if tolerated to 5 mg once daily for 1–2 weeks, then increased if tolerated to 10 mg once daily. Prior to starting treatment, patients should have stable chronic heart failure without acute failure during the past six weeks. For those patients receiving cardiovascular drug therapy including diuretics and/or digoxin and/or ACE inhibitors and/or angiotensin II antagonists, these drugs should be maintained at a stable dose for the two weeks leading up to initiation of Nebivolol treatment. The initiation of therapy and all increases in dose should be carried out 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 heart failure) remains stable. During the initial dose increasing 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 sever 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 led to a transitory worsening of heart failure. If discontinuation is necessary, the dose should be decreased step-wise weekly. **Geriatric Patients:** It is not necessary to adjust the dose in the elderly. **CYP2D6 Polymorphism:** No dose adjustments are necessary for patients who are CYP2D6 poor metabolizer. **Overdosage:** 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, Nebivolol should be stopped and general supportive and specific symptomatic treatments Should be provided. **Missed dose:** Advise patients to take Nebivolol regularly and continuously, as directed. Nebivolol can be taken with or without food. If a dose is missed, take the next scheduled dose only (without doubling it). Do not interrupt or discontinue Nebivolol without consulting the physician.

INSTRUCTIONS:

Dosage as directed by the physician. Store at 25°C, excursions permitted to 15°C -30°C. Protect from sunlight and moisture.
Keep all medicines out of the reach of children.

PRESENTATION

NEBILOL (Nebivolol HCl) 2.5mg tablets are available in Alu-Alu blister pack of 14's with leaflet.
NEBILOL (Nebivolol HCl) 5mg tablets are available in Alu-Alu blister pack of 14's with leaflet.
NEBILOL(Nebivolol HCl) 10mg tablets are available in Alu-Alu blister pack of 14's with leaflet.

علامات/طریقہ استعمال:

نیبیلول ٹیبلٹ کھانے کے ساتھ یا بغیر کھانے کے مندرجہ ذیل علامات میں تجویز کردہ ہے۔

ہائی بلڈ پریشر کے مریضوں میں ہارٹ فیلیئر اور اس سے فسلک اسٹروک، مائیوکارڈیل انفارکشن کے خدشے کو کم کرنے کے لئے استعمال کی جاتی ہے۔

نیبیلول ٹیبلٹ کی ابتدائی خوراک ۲.۵ ملی گرام ہے اور زیادہ سے زیادہ خوراک ۱۰ ملی گرام ہے جو کہ مختلف انفیکشن کی نوعیت کے پیش نظر ڈاکٹر کی ہدایات کے مطابق تجویز کردہ ہے۔

نیبیلول ۱۸ سال سے کم عمر بچوں، پیچیدہ جگر، گردے اور ڈائیلیسز کے مریضوں میں تجویز کردہ نہیں ہے۔

مضر اثرات: ڈیپریشن، سر درد، چکر، قبض، اُلٹی، خارش، تھکن اور دست وغیرہ۔

احتیاطی تدابیر: حاملہ خواتین احتیاط سے استعمال کریں۔

β-blocking ایجنٹ سے مشروط حساسیت رکھنے والے مریض احتیاط سے استعمال کریں۔ دوا کے استعمال کو بتدریج ختم کریں۔

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

۲۵ ڈگری سینٹی گریڈ تک رکھیں محفوظ رکھنے کی حد ۱۵ سے ۳۰ ڈگری سینٹی گریڈ ہے۔

سورج کی روشنی اور نمی سے محفوظ رکھیں۔

تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔ صرف رجسٹرڈ ڈاکٹر کے نسخہ پر فروخت کریں۔

For detailed information please contact:

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