Danlol™
(Nebivolol Hydrochloride)
Tablets

2.5mg
5mg
10mg

ڈینلول
(نیبی ولول ہائیڈروکلورائیڈ)
ٹیبلٹس

۲.۵ ملی گرام
۵ ملی گرام
۱۰ ملی گرام

**QUALITATIVE AND QUANTITATIVE COMPOSITION**
**Danlol™ 2.5mg Tablets:**
Each tablet contains:
Nebivolol HCl equivalent to Nebivolol .....2.5mg
Innovator's Specs.
**Danlol™ 5mg Tablets:**
Each tablet contains:
Nebivolol HCl equivalent to Nebivolol .....5mg
Innovator's Specs.
**Danlol™ 10mg Tablets:**
Each tablet contains:
Nebivolol HCl equivalent to Nebivolol .....10mg
Innovator's Specs.

**DESCRIPTION:** Nebivolol is a racemate composed of d-Nebivolol & 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 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. **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. **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.

**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. Danlol(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 contraindicated in: • Sick sinus syndrome, including sinoatrial 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. 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 or antiarrhythmic agents.
**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. **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. **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.

**PRECAUTIONS:** Abrupt Cessation of Therapy, Angina and Acute Myocardial Infarction, Bronchospastic Diseases, Anesthesia and Major Surgery,Diabetes and Hypoglycemia, Thyrotoxicosis, Peripheral Vascular Disease, Non-dihydropyridine Calcium Channel Blockers, Use with CYP2D6 Inhibitors, Impaired Renal Function, Impaired Hepatic Function, Risk of Anaphylactic Reactions, Pheochromocytoma

**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:** Danlol 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.

**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:**

Danlol™ (Nebivolol as HCl) 2.5mg tablets are available in Alu-Alu blister pack of 1X14's.

Danlol™ (Nebivolol as HCl) 5mg tablets are available in Alu-Alu blister pack of 1X14's.

Danlol™ (Nebivolol as HCl) 10mg tablets are available in Alu-Alu blister pack of 1X14's.

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

۲۵ ڈگری سینٹی گریڈ پر 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۔

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