Pheochromocytoma
In patients with known or suspected pheochromocytoma, initiate an α-blocker prior to the use of any β-blocker.

CONTRAINDICATIONS
- 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)
- Hypersensitive to any component of this product

STORAGE CONDITIONS AND OTHER INFORMATION
- Store below 30°C in a dry place, protect from light.
- To be dispensed on the prescription of a registered medical practitioner only.
- Keep out of the reach of children.

PRESENTATION
Dynalol 2.5 mg tablet is available in blister pack of 10's and 30's.
Dynalol 5 mg tablet is available in blister pack of 10's and 30's.
Dynalol 10 mg tablet is available in blister pack of 10's and 30's.

ہدایات:
- خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
- دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر روشنی سے بچا کر خشک جگہ پر رکھیں۔
- صرف رجسٹرڈ ڈاکٹر کے نسخے پر ہی فروخت کریں۔
- بچوں کی پہنچ سے دور رکھیں۔

Manufactured by:
Kaizen Pharmaceuticals (Pvt.) Ltd.
E-127-129, North Western Industrial Zone,
Bin Qasim, Karachi-75020, Pakistan.

ART No: 684

Dynalol®
(Nebivolol)

ڈائنالول
(نیبی ولول)

2.5mg, 5mg and 10mg Tablets

۲.۵ ملی گرام، ۵ ملی گرام اور ۱۰ ملی گرام گولیاں

Dynalol 2.5mg Tablets
Each tablet contains:
Nebivolol Hydrochloride Eq. to
Nebivolol 2.5mg

Dynalol 5mg Tablets
Each tablet contains:
Nebivolol Hydrochloride Eq. to
Nebivolol 5mg

Dynalol 10mg Tablets
Each tablet contains:
Nebivolol Hydrochloride Eq. to
Nebivolol 10mg

CLINICAL PHARMACOLOGY
Pharmacodynamics:
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, **Dynalol** 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 **Dynalol** 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 renin activity
- 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 (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. Dynalol 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 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.

EFFECTS OF THIS MEDICINE
Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen 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. 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.

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

Usual dose:
Hypertension
The dose of **Dynalol** 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. **Dynalol** 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. Dynalol has not been studied in patients with severe hepatic impairment and therefore it is not recommended in that population.

Subpopulations
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 metabolizers. The clinical effect and safety profile observed in poor metabolizers were similar to those of extensive metabolizers.

Overdose:
In clinical trials and worldwide postmarketing experience there were reports of Nebivolol overdose. The most common signs and symptoms associated with Dynalol overdosage are bradycardia and hypotension. Other important adverse reactions reported with Dynalol overdose include cardiac failure, dizziness, hypoglycemia, fatigue and vomiting. Other adverse reactions associated with β-blocker overdose include bronchospasm and heart block.
The largest known ingestion of **Dynalol** worldwide involved a patient who ingested up to 500 mg of **Dynalol** along with several 100 mg tablets of acetylsalicylic acid in a suicide attempt. The patient experienced hyperhydrosis, pallor, depressed level of consciousness, hypokinesia, hypotension, sinus bradycardia, hypoglycemia, hypokalemia, respiratory failure and vomiting. The patient recovered. 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 Dynalol, 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.

WARNING AND 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. 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 β-blockers, when discontinuation of Dynalol is planned, carefully observe and advise patients to minimize physical activity. Taper Dynalol over 1 to 2 weeks when possible. If the angina worsens or acute coronary insufficiency develops, re-start Dynalol promptly, at least temporarily.

Angina and Acute Myocardial Infarction
Dynalol 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 beta-blockers should generally continue treatment throughout the perioperative period. If Dynalol 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 Dynalol 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. 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 **Dynalol** may need to be reduced.

Impaired Renal Function
Renal clearance of Nebivolol is decreased in patients with severe renal impairment. **Dynalol** has not been studied in patients receiving dialysis.

Impaired Hepatic Function
Metabolism of nebivolol is decreased in patients with moderate hepatic impairment. **Dynalol** 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.