# Anvol® Tablets
(Nebivolol)

عینوال ٹیبلیٹس

**QUALITATIVE & QUANTITATIVE COMPOSITION**

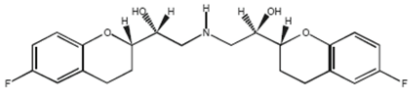
**Anvol tablets 2.5mg:**
Each tablet contains
Nebivolol (as HCl)..... 2.5 mg

**Anvol tablets 5mg:**
Each tablet contains
Nebivolol (as HCl)..... 5mg

**Anvol tablets 10mg:**
Each tablet contains
Nebivolol (as HCl)..... 10mg

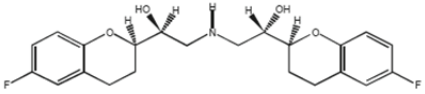
**DESCRIPTION**

The chemical name for the active ingredient in Anvol is Nebivolol. Chemically, it is (1RS,1'RS)-1,1'- [(2RS,2'SR)bis(6- fluoro-3,4-dihydro -2H-1-benzopyran-2-yl)]-2,2'- iminodiethanol hydrochloride. Anvol (Nebivolol) is a racemate composed of d-Nebivolol and l-Nebivolol with the stereochemical designations of [SRRR]-Nebivolol and [RSSS] nebivolol, respectively. Nebivolol's molecular formula is ($C_{22}H_{26}ClF_2NO_4$•HCl) with the following structural formula:



• HCl

**SRRR - or d-Nebivolol hydrochloride**



• HCl

**RSSS - or l-Nebivolol hydrochloride**

**CLINICAL INFORMATION**

**Indications**

• Anvol (Nebivolol) is indicated for the treatment of hypertension, to lower blood pressure. Anvol (Nebivolol) may be used alone or in combination with other antihypertensive agents. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.

• Chronic Heart Failure: treatment of stable mild and moderate chronic heart failure in addition to standard therapies in elderly patients ≥ 70 years.

**Dosage and Administration**

***Hypertension***

The dose of Anvol (Nebivolol) 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. Anvol (Nebivolol) is not known 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. Anvol (Nebivolol) is not known in patients with severe hepatic impairment and therefore it is not recommended.

***Dosage Adjustment***

*Pediatric Use*

Safety and effectiveness in pediatric patients have not been established.

*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.

**Contraindications**

Nebivolol 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

**Warnings 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 may occur 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 Nebivolol is planned, carefully observe and advise patients to minimize physical activity. Taper Nebivolol over 1 to 2 weeks when possible. If the angina worsens or acute coronary insufficiency develops, re-start Nebivolol promptly, at least temporarily.

***Angina and Acute Myocardial Infarction***

Data regarding the use of Nebivolol is not available 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 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.

***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.

***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 is not known in patients receiving dialysis.

***Impaired Hepatic Function***

Metabolism of Nebivolol is decreased in patients with moderate hepatic impairment. Nebivolol is not known 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.

**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.

**Pregnancy and Breastfeeding**

*Category C*

Use Nebivolol during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because of the potential for β-blockers to produce serious adverse reactions in nursing infants, especially bradycardia, Nebivolol is not recommended during nursing.

**Adverse Reactions**

The most common adverse reactions that can lead to discontinuation of Nebivolol are headache, nausea and bradycardia.

***Body as a Whole:*** asthenia.

***Gastrointestinal System Disorders:*** abdominal pain

***Metabolic and Nutritional Disorders:*** hypercholesterolemia, increased BUN, increased triglycerides, decreased HDL and low platelets.

***Nervous System Disorders:*** paraesthesia

**Overdose**

The most common signs and symptoms associated with Nebivolol overdosage are bradycardia and hypotension. Other important adverse reactions that may occur with Nebivolol overdose 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.

**PHARMACOLOGICAL PROPERTIES**

**Pharmacotherapeutic group:** Beta blocking agent, selective.

ATC code: C07AB12

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.

**Pharmacokinetic Properties**

***Absorption***

Nebivolol is rapidly absorbed after oral doses. Mean peak plasma Nebivolol concentrations occur approximately 1.5 to 4 hours post-dosing.

***Distribution***

Human plasma protein binding of Nebivolol is approximately 98%, mostly to albumin, and is independent of Nebivolol concentrations.

***Metabolism***

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.

***Elimination***

It is excreted in the urine and faeces, almost entirely as metabolites.

**PHARMACEUTICAL INFORMATION**

**Shelf Life**

2 years.

**Special Precautions for Storage**

- To be sold on the prescription of a registered medical practitioner only.
- Do not store above 30ºC.
- Protect from light and moisture.
- Keep out of the reach of children.

**ہدایات:**

صرف مستند ڈاکٹر کے نسخے پر فروخت کریں۔
۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں۔
دوا کو روشنی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

**Nature and contents of container**

- Anvol (Nebivolol) 2.5 mg tablets are available in a blister of 14's (1x14's).
- Anvol (Nebivolol) 5 mg tablets are available in a blister of 14's (1x14's).
- Anvol (Nebivolol) 10 mg tablets are available in a blister of 14's (1x14's).

**MANUFACTURED BY**

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**REVISION DATE**

February 2020