Bystolic™

Drug Particulars

Generic name: Nebivolol Hydrochloride
Synonym(s): Nebivolol, hidrocloruro de; R-067555; R-67555
Chemical name: (1 RS, 1 'RS)-III ' -[(2RS,2'SR)-bis(6-fluoro-3,4-dihydro-2H-1 -benzopyran-2-yl)]-2,2'-iminodiethanol hydrochloride
Brand name: Bystolic™
Manufacturer: Forest Pharmaceuticals Incorporated
CAS number: 99200-09-6; 118457-14-0
Therapeutic classification: Martindale – Cardiovascular drugs; BNF – Beta-adrenoceptor blocking drugs
Legal classification: Prescription only

Physical Properties

Molecular formula: C_{22}H_{25}F_{2}NO_{4},HCl
Structural formula: Nebivolol is a racemate of d-nebivolol and l-nebivolol with the stereochemical designations of [SRRR]-nebivolol and [RSSS]-nebivolol

Molecular weight: 441.9g/mol
Appearance: White to almost-white powder
Solubility: Nebivolol is soluble in N,N-dimethylformamide, methanol, dimethylsulfoxide; sparingly soluble in polypropylene glycol, polyethylene glycol and ethanol; and very slightly soluble in dichloromethane, hexane and methylbenzene
Preparation(s): Bystolic™ tablets are triangular-shaped, biconvex, unscored, differentiated by color and are engraved with "FL" on one side and the number of mg (2.5, 5, or 10) on the other side

<table>
<thead>
<tr>
<th>Tablet Strength</th>
<th>Package Configuration</th>
<th>Tablet Colour</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5mg</td>
<td>30 tablets per bottle</td>
<td>Light Blue</td>
</tr>
<tr>
<td></td>
<td>100 tablets per bottle</td>
<td></td>
</tr>
<tr>
<td>5mg</td>
<td>30 tablets per bottle</td>
<td>Beige</td>
</tr>
<tr>
<td></td>
<td>100 tablets per bottle</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 x 10 unit dose</td>
<td></td>
</tr>
<tr>
<td>10mg</td>
<td>30 tablets per bottle</td>
<td>Pinkish-purple</td>
</tr>
<tr>
<td></td>
<td>100 tablets per bottle</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 x 10 unit dose</td>
<td></td>
</tr>
</tbody>
</table>
**Recommended Dosage**

**General population**
The recommended initial dose is Bystolic™ 5mg once daily.\(^1,2,4\) It may be increased at a 2-week interval up to 40mg once daily for any inadequate control of blood pressure. More frequent dosing does not improve the effectiveness. It can be used as monotherapy or in combination with other antihypertensives.\(^1\)

**Renal impairment**
The recommended initial dose for patients with moderate renal impairment is Bystolic™ 2.5mg once daily.\(^1,2,4\) The dose can be titrated up with caution if required. The maximum dose is 5mg once daily. The dose should be adjusted in patients with severe renal impairment.\(^1,2\) Bystolic™ has not been studied in patients receiving dialysis.

**Hepatic impairment**
The recommended initial dose for patients with moderate hepatic impairment is Bystolic™ 2.5mg once daily. The safety and efficacy of Bystolic™ in patients with severe hepatic impairment have not been established and thus is contraindicated.\(^1\)

**Geriatric**
It is not necessary to adjust the dose in the elderly.\(^1\) However, some references recommend a lower initial dose of 2.5mg once daily and titration to 5mg once daily if necessary.\(^2,4\)

**Pediatric**
The use of Bystolic™ in patients from newborns to adolescents is not well studied because of the potential developmental abnormalities and adverse effects on fertility. The effectiveness is also unknown. So it is not recommended that patients from 0 to 18 years old take Bystolic™.\(^1,5\)

**Pregnancy\(^1,5\)**

**Pregnancy Category C**
In general, beta-adrenoceptor blocking agents reduce placental perfusion and may be associated with growth retardation, intrauterine death, abortion and early labour. Hypoglycemia and bradycardia may occur within the first 3 days in the newborns.

Exposure to 1.25-2.5mg/kg nebivolol during prenatal period resulted in decreased pup weight in rats. At 5mg/kg and higher doses ([1.2 times the maximum recommended human dose (MRHD)], prolonged gestation, dystocia, increases in fetal deaths and stillbirths, decreased birth weight and live litter size were noticed. The pup survival was so low that there were insufficient pups for analyzing the effect of nebivolol on long-term fertility.

At doses as high as 20mg/kg (10 times the MRHD) in pregnant rabbits, no adverse effects on embryo-fetal viability, sex, weight and morphology were identified. At 20 and 40mg/kg nebivolol given to pregnant rats during organogenesis, reduced birth weight was found; at 40mg/kg, small reversible delays in sternal and thoracic ossification and slightly increased resorption were noticed.

As a result, Bystolic™ should not be used in pregnant women unless absolutely necessary and the benefit outweigh the risk; uteroplacental perfusion, the fetus and the newborn must be monitored closely.

**Lactation**
Bystolic™ and its metabolites pass the placenta and are excreted in breast milk in rats but its excretion into the human milk is unknown. Breastfeeding is not recommended during its administration.\(^1\)

**Storage condition**
Store the medication in a cool and dry place at 20-25°C.
Bioavailability/Pharmacokinetics

Absorption
Rapidly absorbed after oral doses.

Distribution
Nebivolol is distributed into breast milk in animals. No tissue specific distribution data can be revealed.

Metabolism
Nebivolol undergoes extensive hepatic metabolism predominantly via glucuronidation and to a lesser extent N-dealkylation and oxidation by cytochrome P450 2D6. Genetic polymorphism is observed in its metabolism via CYP2D6. The hydroxy metabolites are reported to be active.

Excretion
Almost all Nebivolol is excreted as oxidative metabolites or glucuronide conjugates after a single oral administration. The excretion pattern for:

- *Extensive metabolizers* – 38% in urine and 44% in faeces
- *Poor metabolizers* – 67% in urine and 13% in faeces

<table>
<thead>
<tr>
<th></th>
<th>Extensive Metabolizers</th>
<th>Poor Metabolizers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Half-life</strong></td>
<td>~12 hours</td>
<td>19 hours</td>
</tr>
<tr>
<td><strong>T&lt;sub&gt;max&lt;/sub&gt;</strong></td>
<td>1.5 hours</td>
<td>4 hours</td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt;</strong></td>
<td>5 times higher for poor metabolizers than extensive metabolizers</td>
<td></td>
</tr>
<tr>
<td><strong>AUC</strong></td>
<td>10 times higher for poor metabolizers than extensive metabolizers</td>
<td></td>
</tr>
</tbody>
</table>

Bioavailability:
Absolute bioavailability has not been determined. For doses up to 20mg, the plasma level increases proportionally with the dose.

Protein binding
About 98% protein bound, mostly to albumin, during *in vitro* testings. The level of binding is independent of the drug concentration.

Known Adverse Effects

*Events Observed During Worldwide Clinical Trials (with incidence ≥ 1%)*

- **Body as a whole** – asthenia
- **GI Disorder** – abdominal pain
- **Metabolic and Nutritional Disorders** – hypercholesterolemia, hyperuricemia
- **Nervous System Disorders** – paraesthesia
- **Laboratory** – Increased BUN, uric acid and triglycerides
  
  Decrease in HDL cholesterol and platelet count

*Most Common Adverse Events leading to Discontinuation*

Headache (0.4%), nausea (0.2%) and bradycardia (0.2%).
Special Precautions
Dosage adjustment is needed for the elderly (>65 years old) and renal compromised patients. The initial
dose of Nebivolol should be reduced to 2.5 mg once daily for the management of hypertension.2

As of all other beta-blockers, Nebivolol should be used with cautions in patients with 1st degree AV block,
portal hypertension, history of obstructive airway disease, myasthenia gravis, and history of
hypersensitivity response. It may also mask the symptoms of hypoglycemia and thyrotoxicosis. Abrupt
withdrawal should be avoided especially in patients with ischemic heart disease.4

Users should also be aware that the use of Nebivolol (along with other beta-blockers) is prohibited in
certain sports,7 either in-competition and/or off-competition. For further details, please consult your local
sport authorities or visit the website of World Anti-doping Agency: http://www.wada-ama.org

Contraindications
Nebivolol, same as other beta-blockers, is contraindicated in patients with asthma, uncontrolled heart
failure, marked baddycardiac and hypotension, Prinzmetal’s angina, sick sinus syndrome, 2nd and 3rd
degree AV block, cardiogenic shock, metabolic acidosis, severe peripheral arterial disease and
phaeochromocytoma. It is also contraindicated in patients with hepatic impairmen,t4,2,8 as well as lactating
and pregnant women.8

Drug Interactions

Drug-Drug Interactions4

- ACEI – enhanced hypotensive effect
- adrenergic neurone blocker – enhanced hypotensive effect
- alcohol – enhanced hypotensive effect
- aldesleukin – enhanced hypotensive effect
- alpha blocker – enhanced hypotensive effect; also increase risk of first dose hypotension with post–
synaptic alpha blockor such as prazosin
- general anaesthetic – enhanced hypotensive effect
- analgesic – hypotensive effect antagonized by NSAID
- angiotensin-II receptor antagonist – enhanced hypotensive effect
- anti-arrhythmics – increase myocardial depression; increase risk of bradycardia, AV block and
myocardial depression with amiodarone; increase risk of bradycardia and
myocardial depression with flecaainide
- antidiabetics – may mask warning sign of hypoglycaemia (such as tremor); enhance hypoglycaemic
effect of insulin
- antimalarials – increase risk of bradycardia with mefloquine
- antipsychotic – enhance hypotensive effect with phenothiazines
- anxiolytics and hypnotic – enhance hypotensive effect
- calcium channel blocker – enhance hypotensive effect; possible severe hypotension and heart failure
with nifedipine or nisoldipine; increase risk of AV block and bradycardia
with diliazem; asystole, severe hypotension and heart failure with
verapamil
- cardiac glycoside – increase risk of AV block and bradycardia
- clonidine – increase risk of withdrawal hypertension with clonidine, to reduce the risk, withdraw
Nebivolol several days before slowly withdraw clonidine
- corticosteroids – hypotensive effect antagonized by corticosteroid
- diazoxide – enhance hypotensive effect
• diuretics – enhance hypotensive effect
• dopaminergics – enhance hypotensive effect with levodopa
• ergot alkaloids – increase peripheral vasoconstriction with ergotamine and methysergide
• 5HT₁ antagonist – increase risk of ventricular arrhythmias with tropiseton
• methyldopa – enhance hypotensive effect
• moxisylyte – possible severe postural hypotension
• moxonidine – enhance hypotensive effect
• muscle relaxant – enhance hypotensive effect with baclofen; possible enhanced hypotensive effect and bradycardia with tizanidine
• nitrates – enhance hypotensive effect
• oestrogen – hypotensive effect antagonized by oestrogen
• pilocarpine – increase risk of arrhythmia
• alprostadil – enhance hypotensive effect
• sympathomimetics – severe hypertensive effect with adrenaline, noradrenaline or dobutamine
  vasodilator antihypertensive: enhance hypotensive effect with hydralazine, minoxidil or sodium nitroprusside

Drug-Food Interactions
Food does not alter the pharmacokinetics of nebivolol but under fed conditions, Nebivolol glucuronides are slightly reduced. Bystolic may be administered without regarding to meals.

Patient Monitoring Guidelines
To ensure the efficacy of Nebivolol in antihypertensive management, blood pressure should be monitored regularly. Additional antihypertensive agents may be required provided if the blood pressure is not well controlled.

The adverse reactions of Nebivolol are generally tolerable, but patients should consult the physicians if significant adverse effects, for instance hypotension, difficulty in breathing due to bronchospasm, bradycardia, increasing shortness of breath and weight as the symptoms of deteriorating heart failure, are experienced.²,⁹ These may be the consequence of overdosing and dosage adjustment is required. Owing to the cardiovascular effects of Nebivolol, concurrent use of medications affecting the myocardial cell and atrioventricular conduction, for example calcium channel blocker and anti-arrhythmic drugs, should also be closely monitored.¹⁰

Beta-blocker is not contraindicated for diabetic patients, but it can affect glucose tolerance and mask the symptoms of hypoglycaemia. Thus, the effect of Nebivolol in diabetic patients should be monitored and appropriate dosage adjustment should be considered if necessary.²,⁴

The effects of Nebivolol in patients with renal and hepatic impairment should be closely monitored as these may affect the drug metabolisms or excretions. Dosage adjustment is also required.²,⁹

Patient Information
Before taking Nebivolol, make sure your doctor or pharmacist knows: ¹¹
• if you are pregnant, planning to have a baby or breast-feeding
• if you have any hepatic or renal problems
• if you suffer from low blood pressure or poor circulation
• if you have diabetes
• if you suffer from asthma or breathing difficulties
• if you have any allergic reaction to certain medicines
• if you are currently taking any other medicines, including OTC products, herbal and complementary medicines

Patients should know how they react to this medicine before they operate automobiles, use machinery, or engage in other tasks requiring alertness.7

Nebivolol should be used with caution in patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, because beta-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia.7

**Taking Nebivolol**

• Patients should be advised to take Bystolic regularly and continuously, as directed by your doctor7
• Always read the manufacturer's information leaflet, if possible, before beginning treatment11
• Best to take nebivolol at the same times each day to avoid missing any doses
• If a dose is missed, the patient should take the next scheduled dose only (without doubling it)7
• Never take more than the prescribed dose11
• Never give the drug to others even if their condition appears to be the same as yours12

**During treatment**11,12

• Consult your pharmacist before taking any 'over-the-counter' medicines
• Keep your regular doctors appointments so your progress can be monitored
• Before having any kind of surgery, including dental or emergency treatment, tell the doctor, dentist or surgeon that you are taking nebivolol
• Any dietary advice that you may have been given by your doctor should be followed
• Check your blood glucose levels regularly as this preparation can affect the levels of sugar in your blood if you have diabetes
• Patients should be advised to consult a physician if any difficulty in breathing occurs, or if they develop signs or symptoms of worsening congestive heart failure such as weight gain or increasing shortness of breath, or excessive bradycardia
• Along with their useful effects, all medicines can cause unwanted side effects, which usually improve as your body adjusts to the new medicine
• When encountering any severe side effects (described in the part of side effects), consult your doctor or pharmacist immediately

**How to store Nebivolol**11,12

• No special storage precautions are required
• Keep all medicines out of the reach of children
• Store in a cool dry place, away from direct heat and light
• Never keep out of date or unwanted medicines. Discard them safely out of the reach of children or take them to your local pharmacist who will dispose of them for you
• Do not use after the expiry date on the box or on the blister

### Comparison between the efficacy of Nebivolol and other beta-blockers

1. *Nebivolol vs Bisoprolol (multicentre, RCT)*13

<table>
<thead>
<tr>
<th></th>
<th>Nebivolol</th>
<th>Bisoprolol</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td>−20.5 ± 12.9</td>
<td>−20.0 ± 12.0</td>
<td>0.7434</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>−15.7 ± 6.4</td>
<td>−16.0 ± 6.8</td>
<td>0.8230</td>
</tr>
<tr>
<td>Baseline HR</td>
<td>74.4 ± 9.6</td>
<td>74.4 ± 8.7</td>
<td>NA</td>
</tr>
<tr>
<td>HR at the end of test</td>
<td>68.7 ± 8.5</td>
<td>68.1 ± 7.5</td>
<td>NA</td>
</tr>
</tbody>
</table>
2. Nebivolol vs Atenolol (RCT)\textsuperscript{14}

Table 2: Blood pressure and heart rate change from baseline (Week 0) after 2 and 24 weeks of treatment with nebivolol or atenolol.

<table>
<thead>
<tr>
<th></th>
<th>Nebivolol (n = 15)</th>
<th>Atenolol (n = 15)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wk 0       Wk 2       Wk 24</td>
<td>Wk 0      Wk 2       Wk 24</td>
<td>Wk 0      Wk 2       Wk 24</td>
</tr>
<tr>
<td>Supine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>104.9  -19.2  -25.7</td>
<td>102.3  -12.9  -17.9</td>
<td>NS       NS       NS</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>81.1    -10.4  -14.4</td>
<td>80.4    -11.1  -13.3</td>
<td>NS       NS       NS</td>
</tr>
<tr>
<td>HR (b/min)</td>
<td>101.2  -10.6  -15.6</td>
<td>101.9  -18.3  -27.7</td>
<td>NS       NS       NS</td>
</tr>
<tr>
<td>Standing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>105.7  -13.2  -18.0</td>
<td>105.5  -11.9  -18.7</td>
<td>NS       NS       NS</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>80.9    -12.3  -15.6</td>
<td>84.1    -12.0  -13.3</td>
<td>NS       NS       NS</td>
</tr>
<tr>
<td>HR (b/min)</td>
<td>101.5  -10.6  -15.6</td>
<td>101.9  -18.3  -27.7</td>
<td>NS       NS       NS</td>
</tr>
</tbody>
</table>

*Mann–Whitney U-test for between treatment differences in changes from end of run-in.

Note: BP and HR reductions from end of run-in to week 24 were highly significant within each treatment group (P < 0.001 Friedman test).

3. Nebivolol vs Metoprolol\textsuperscript{15}

Fig. 2: Changes in systolic and diastolic blood pressure (SBP and DBP respectively) in Treatment group A (period 1 nebivolol 5 mg once daily, period 2 metoprolol 95 mg once daily, n = 25; \textcircled{1}) and Treatment group B (period 1 metoprolol succinate 95 mg once daily, period 2 nebivolol 5 mg once daily, n = 25; \textcircled{2}). Both \(\beta\)-adrenoceptor antagonists similarly decreased SBP and DBP in hypertensive men. *P < 0.05 compared with time 0 in Treatment group A; \(^{1}\)P < 0.05 compared with time 0 in Treatment group B.
4. Nebivolol vs Nifedipine (Multicenter Study. RCT)\textsuperscript{16}

<table>
<thead>
<tr>
<th></th>
<th>Nebivolol</th>
<th>Nifedipine</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in DBP (mm Hg)</td>
<td>-11.7</td>
<td>-10.9</td>
<td>NA</td>
</tr>
<tr>
<td>Change in HR (per minute)</td>
<td>-7.6 ± 0.69</td>
<td>insignificant</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

5. Nebivolol vs Enalapril (Multicenter Study. RCT)\textsuperscript{17}

<table>
<thead>
<tr>
<th></th>
<th>Nebivolol</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in DBP (mm Hg)</td>
<td>-12.3</td>
<td>-9.9</td>
</tr>
<tr>
<td>Baseline HR</td>
<td>similar</td>
<td></td>
</tr>
<tr>
<td>HR after 12 weeks</td>
<td>68.7±0.69</td>
<td>74.5±0.81</td>
</tr>
</tbody>
</table>

Comparison between the safety of Nebivolol and other beta-blockers

1. Nebivolol vs Atenolol

In a double-blind, randomized, parallel group, placebo-controlled trial, 364 primary care patients in the United Kingdom with mild-to-moderate hypertension (diastolic BP = 95 mm Hg and systolic BP = 115 mm Hg) were randomized for 1 month to nebivolol 5 mg/day (n = 119), atenolol 50 mg/day (n = 121), or placebo (n = 124). The rates of adverse effects, of which headache, dizziness, and fatigue were most frequent, were similar with atenolol, nebivolol, and placebo. However, reported incidences of fatigue and decreased interest in sexual activity were higher with atenolol than with nebivolol or placebo.\textsuperscript{18}

<table>
<thead>
<tr>
<th></th>
<th>placebo</th>
<th>nebivolol</th>
<th>atenolol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BL (n = 124)</td>
<td>DB (n = 124)</td>
<td>BL (n = 119)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Headache</td>
<td>5</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Per cent of patients with AE</td>
<td>23</td>
<td>25</td>
<td>22</td>
</tr>
</tbody>
</table>

Table 1  Adverse experiences (AE) reported in at least three patients (BL = baseline; DB = double-blind): number of patients studied in each group shown
Nebivolol was also compared to atenolol in a double-blind, randomized, multicenter study in 205 men and women with mild-to-moderate hypertension, who were randomized to nebivolol 5 mg (n = 105) or atenolol 100 mg (n = 100) once daily for 12 weeks. The incidence of adverse effects, however, was significantly higher with atenolol, either when spontaneously reported (P = .049) or when reported on a questionnaire (P < .001) (Fig. 1).19

Fig. 1  The incidence of adverse effects (AEs) was significantly lower with nebivolol than with atenolol in a double-blind, randomized, multicenter study in 205 men and women with mild-to-moderate hypertension

2. Nebivolol vs Metoprolol
In a randomized, double-blind, multicenter trial, 140 patients with mild-to-moderate hypertension (sitting diastolic BP >100 mm Hg) were given nebivolol 5 mg once daily (n = 73) or metoprolol 100 mg twice daily (n = 67) for 3 months. However, fewer adverse effects were reported in the nebivolol group (23%) than in the metoprolol group (36%), compared with 21% during the preceding placebo phase.20

Cost Comparison

The price of Nebivolol as compared with other currently used β-blockers

<table>
<thead>
<tr>
<th>Dose*</th>
<th>Cost (28 days)#</th>
<th>HK Cost (28 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nebivolol 5 mg daily</td>
<td>£9.80</td>
<td>$151.9</td>
</tr>
<tr>
<td>Atenolol 50 mg daily</td>
<td>£1.22</td>
<td>$19.0</td>
</tr>
<tr>
<td>Bisprolol 10 mg daily</td>
<td>£9.61</td>
<td>$179</td>
</tr>
<tr>
<td>Carvedilol 25 mg daily</td>
<td>£13.15</td>
<td>$168</td>
</tr>
</tbody>
</table>

*Dose is recommended for the treatment of the essential hypertension in normal adult
#Cost is defined in Drug Tariff in UK NHS system

Reference
1 Bystolic™ Prescribing Information, Forest Pharmaceuticals Inc., 12/2007


3 Bystolic™, Drug@FDA, Food and Drug Administration


5 Nebilet SPC, The Medicines Compendium (electronic version), The Association of British Pharmaceutical Industry


12 Electronic Medicines Compendium. Product information leaflet of Nebilet 5mg tablets.


