

## Bystolic (nebivolol) STEPS

### Recommendation

Additional studies are needed with nebivolol in patients with heart failure and coronary artery disease as well as outcomes data. It is an option for the treatment of hypertension; however, many well established more cost-effective beta blockers alternatives are available.

### Approved by the FDA December 17, 2007 (Forest)

Nebivolol is a highly selective inhibitor of beta-1-adrenergic receptors and has vasodilatory effects. **It retains this selectivity up to 10mg.** Nebivolol is a racemic mixture made up of equal parts of the D- (beta blocking properties) and L- (endothelium-dependent vasodilating properties) isomers.

It produces vasodilation by acting as a beta-3 receptor agonist, which increases the activity of nitric oxide synthase and subsequently increases nitric oxide production. Nitric oxide activity is also augmented by nebivolol through the prevention of nitric oxide deactivation. Carvedilol and labetalol causes vasodilation through its effects on  $\alpha_1$ -adrenoceptors.

In extensive metabolizers (EMs) and at doses  $\leq 10\text{mg}$ , nebivolol is preferential to  $\beta_1$ -adrenergic. In poor metabolizers (PMs) and at higher doses, nebivolol inhibits both receptors.

Mechanism of action of the antihypertensive response has not been definitely established.

### Indications

Bystolic is indicated for the treatment of hypertension, alone or in combination with other antihypertensive agents.

### Safety =/— (new agent)

*Sound-alike/Look-alike:* None noted.

### Drug Interactions:

It is metabolized by hepatic CYP 2D6. When administered with an inhibitor (fluoxetine, paroxetine, quinidine, etc.) or an inducer of this enzyme, patients should be closely monitored and the nebivolol dose adjusted according to blood pressure response. See package insert for recommendations.

### Contraindication:

Contraindicated in patients with severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place) or severe hepatic impairment (Child-Pugh>B), and or hypersensitivity to any component of Bystolic.

### Warnings/Precautions:

- Warnings and precautions with beta blocker therapy apply.
- Beta-blocker therapy should not be stopped abruptly. Medication should be tapered over 1-2 weeks to avoid acute tachycardia, hypertension, and/ischemia.
- Caution should be used in patients on agents that reduce heart rate (calcium channel blockers, digoxin, amiodarone), cardiac contractility (calcium channel blockers, amiodarone) and antiarrhythmic agents. Don't combine with other beta blockers.
- Bystolic was not studied in patients with angina pectoris or who had a recent MI.
- In general, patients with bronchospastic diseases should not receive beta blockers. Beta blockers may mask some manifestations of hypoglycemia and hyperthyroidism, such as tachycardia.

### Renal:

Package insert recommends dosage adjustment in patients with severe renal impairment, based on a single 5mg dose. It should be used with caution in patients receiving dialysis (no formal studies have been conducted).

Hepatic: Nebivolol is primarily hepatically metabolized. The starting dose should be reduced in patients with moderate hepatic impairment. It is contraindicated for patients with severe hepatic impairment (no formal studies have been performed)

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### Children:

Safety and effectiveness of nebivolol has not been established in children.

### Race/Gender/Ethnicity:

Blood pressure reductions greater than placebo in African American have been shown, comparisons to other beta-blockers have not been completed looking at effects in African Americans. In vitro, it has been shown to increase the bioavailability of nitric oxide in the endothelium of African Americans, more than white Americans. Clinical benefit of this finding is not determined.

### Pregnancy:

**Manufacturer: Category Risk Factor C**

**Expert Opinion: Category Risk Factor D (2<sup>nd</sup> and 3<sup>rd</sup> trimester)**

There are no adequate and well controlled studied in pregnant women.

Nursing Mothers: Excretion in breast milk is unknown and use in breast-feeding women is not recommended.

## Tolerability =

Common adverse events in the placebo trials are listed below for incidents with  $\geq 1\%$  in nebivolol treated patients and those that were at a higher frequency than placebo-treated patients.

Adverse Event	Placebo	5mg	10mg	20-40mg
Fatigue %	1	2	2	5
Headache %	6	9	6	7
Dizziness %	2	2	3	4
Nausea %	0	1	3	2
Insomnia %	0	1	1	1
Chest Pain%	0	0	1	1
Bradycardia %	0	0	0	1
Dyspnea %	0	0	1	1
Rash %	0	0	1	1

Comparative studies show adverse effects similar to other beta blockers.

## Efficacy =/— (mortality data)

Nebivolol does provide blood pressure reduction from baseline compared to placebo. Blood pressure reductions similar to atenolol, bisoprolol, amlodipine, nifedipine, lisinopril and hydrochlorothiazide in comparative trials.

### Nebivolol Studies:

Study 1 and 2: Randomized double-blind, multicenter, placebo controlled trials (Doses from 1.25 to 40mg), 12 weeks.

Study 3: Same as 1 and 2, but only black patients enrolled.

Study 4: Placebo controlled trial with doses from 5 to 20mg with other agents (ACE inhibitors, ARBs, and/or thiazide diuretics)

### Comparisons:

Beta-1 selectivity: 3 to 10 times bisoprolol and metoprolol, but no proof that it is safer in asthma patients than other beta-1 selective blockers. Package insert has a caution.

Inotropic properties: Less than metoprolol and carvedilol

Heart rate: Reduces similar to atenolol, bisoprolol, and metoprolol.

Platelet aggregation inhibition: Greater than propranolol or carvedilol.

**Bystolic (nebivolol) STEPS**  
**Sitting Systolic Blood Pressure/Sitting Dystolic Blood Pressure (mg Hg) for Various Doses**

These are placebo-subtracted least-square mean reductions in trough SiSBP/SiDBP (mm Hg) from Study 1, 2 and 3 (n=2016 patients)

Study	1.25mg	2.5mg	5mg	10mg	20mg	30-40
1	<b>-6.6/-5.1</b>	<b>-8.5/-5.6</b>	<b>-8.1/-5.5</b>	<b>-9.2/-6.3</b>	<b>-8.7/-6.9</b>	<b>-11.7/-8.3</b>
2			-3.8/-3.2	-3.1/-3.9	<b>-6.3/-4.5</b>	
3 n=300		-1.5/-2.9	-2.6/-4.9	<b>-6.0/-6.1</b>	<b>-7.2/-6.1</b>	<b>-6.8/-5.5</b>
4			<b>-5.7/-3.3</b>	<b>-3.7/-3.5</b>	<b>-6.2/-4.6</b>	

**P<0.05** based on pair wise comparison vs. placebo in bold

Pooled results of Study 1, 2, and 3 at doses listed (n=1082)

Dose	5mg n=459	10mg n=461	20mg n=460	40mg n=217	Placebo n=205
Baseline	152.0/99.4	152.8/99.3	152.4/99.5	152.6/99.1	152.3/99.8
Result with mean Δ in BP	<b>141.7/89.7</b>	<b>142.1/88.9</b>	<b>140/88.4</b>	<b>141/88.3</b>	148/94.8

**P<0.001** vs. placebo in bold

SENIORS Outcomes Study

(Study of the **E**ffects of **N**ebivolol Intervention on **O**utcomes and **R**ehospitalization in **S**eniors)

Nebivolol was compared with placebo in patients 70 years or older with heart failure with a mean follow-up duration of 21 months. The incidence of all cause mortality and cardiovascular hospital admission was absolutely reduced by 4.2% and relatively reduced by 11.9% in the nebivolol group.

In the SENIORS study, the reduction in death and hospitalization appears to be less than that seen with other beta-blockers studied for heart failure (bisoprolol, carvedilol, and metoprolol). The SENIORS study was with an older population than the other (CIBIS 2, COPERNICUS, and MERIT-HF)

Pharmacokinetics:

Oral absorption ranges from 12% in EMs to 96% in PMs.

Onset: 1 hour

t ½: 0-12 hours in EMs, 19-32 in PMs

Excretion: Urine (EMs 38%, PMs 67%) and feces (EMs 44%, PMs 13%)

**Price — —**

Nebivolol available as 2.5, 5 and 10mg unscored triangular tablets. Maximum daily dosage is 40mg.

	<u>Each</u>	<u>Monthly Cost*</u>
Nebivolol (Bystolic) 5mg	\$1.87 each	\$55.99 (5mg QD)
Nebivolol 10mg	\$1.90 each	\$56.99 (10mg QD)
Carvedilol (Coreg) 3.125, 6.25, 12.5mg	\$0.49	\$29.98 (BID)
Carvedilol 25mg	\$0.53	\$31.99 (BID)
Coreg CR 10mg, 20mg, 40mg, 80mg	\$4.09	\$122.71 (QD)
Labetolol ((Trandate) 100mg	\$0.35	\$20.99 (BID)
Labetalol 200mg	\$0.48	\$28.99 (BID)
Labetalol 300mg	\$0.63	\$38.99 (BID)
Metoprolol (Lopressor) 25-100mg		\$12.99-15.99 (BID)
Atenolol (Tenormin) 25-100mg		\$11.99-17.99 (QD)

\*Drugstore.com

**Simplicity =**

**May be taken without regard to food.** Available as 2.5mg, 5mg, and 10mg unscored triangular-shaped oral tablets. The starting dosage is 5mg once daily. Dosage increases can be done weekly to a maximum of 40mg **once daily**.

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### References

1. Product information for Bystolic. Forest Pharmaceuticals, Inc. St. Louis, MO 63045. December 2007.
2. Kalus JS, Salinitri FD. Nebivolol: a beta agonist with novel pharmacologic properties. *Formulary*. 2004;39:532-41.
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4. Weiss RJ, Weber MA, Carr AA, Sullivan WA. A Randomized, Double-Blind, Placebo-controlled Parallel-Group Study to Assess the Efficacy and Safety of Nebivolol, a Novel  $\beta$ -Blocker, in Patients with Mild to Moderate Hypertension. *J Clin Hypertens*. 2007;9:667-676.
5. Flater MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J*. 2005;26:215-25.