



## Therapeutic Class Review<sup>SM</sup>

### Cardiovascular – nebivolol (Bystolic<sup>TM</sup>)

June 2008

**New Product for Review:**

nebivolol (Bystolic<sup>TM</sup>) [Forest/Mylan]

**Dossier Provided by Manufacturer: Yes**

**Dossier Evaluation: 1**

- 1 - Dossier missing significant clinical trial(s).
- 2 - Mfg. provided all relevant trials; Missing pharmacoeconomic model.
- 3 - Mfg. provided all relevant trials and information.

#### Executive Summary

##### *Hypertension*

- High blood pressure is associated with an increased risk of heart attack, heart failure, stroke, and kidney disease.
- The ultimate goal of antihypertensive therapy is to reduce cardiovascular and renal morbidity and mortality.
- National and International Guidelines recommend a diuretic as initial treatment for hypertension for the majority of patients.<sup>[1]</sup>
- Two-thirds of patients will require two or more agents to achieve optimal control of their blood pressure.<sup>[1]</sup>
- Choice of antihypertensive medications is guided by patient-specific comorbidities.

##### *Nebivolol (Bystolic)*

- Nebivolol (Bystolic) is a new beta-blocker approved for the treatment of hypertension.<sup>[2]</sup>
  - It is the nineteenth beta-blocker approved in the U.S. market.
  - It is taken in doses of 5 mg to 40 mg once per day.
  - Cardioselective properties have been demonstrated in doses up to 10 mg per day.
- Current antihypertensive trials comparing nebivolol (Bystolic) with sugar pills do not support any safety or efficacy advantages over other beta-blockers.
- Nearly all beta-blockers are available as generic products and are preferred/formulary at Regence.
- Bisoprolol, carvedilol and extended-release metoprolol (all generics) have demonstrated benefit in improving cardiovascular morbidity and mortality.
- FDA labeling for nebivolol (Bystolic) is limited to the treatment of hypertension.<sup>[2]</sup>
- Product value for new beta-blockers is best determined via comparison to "gold standard" beta-blockers using cardiovascular morbidity and mortality endpoints.

## **Evidence**

### *Hypertension*

- Evidence from individual studies of nebivolol (Bystolic) in the treatment of hypertension is not reliable.
- Overall, a large body of evidence consistently demonstrates lowering of blood pressure with nebivolol (Bystolic) which increases the likelihood that this effect is due to nebivolol (Bystolic) rather than to chance.
- There is no reliable evidence that nebivolol (Bystolic) is better than other antihypertensive medications, including other beta-blockers, in lowering blood pressure.

### *Other cardiovascular conditions*

- There is no reliable evidence that nebivolol (Bystolic) prevents cardiovascular or renal morbidity or mortality (e.g., prevention of heart attacks, heart failure, stroke, or kidney disease).

### *Safety*

- There is no reliable information comparing the safety of nebivolol (Bystolic) with other beta-blockers.
- The most common adverse effects (AEs) reported with nebivolol (Bystolic) include headache, fatigue, dizziness, nausea, and rash. These are also the most common AEs reported with other beta-blockers.

## **Decision**

Nebivolol (Bystolic) is non-preferred/non-formulary because:

- There are many preferred/formulary antihypertensive options available, including nearly all beta-blockers.
- There is no evidence of additional benefit over current preferred/formulary antihypertensive options.
- There is no reliable evidence that it reduces cardiovascular morbidity or mortality.

## Products

Drug Products	FDA approval <sup>a</sup>	Patent Expiration(s) <sup>b</sup>	Usual Dose/Route	Potential Off-label Uses <sup>c</sup>
acebutolol (generic) <sup>[3]</sup>	12/1984	expired	200 to 600 mg PO twice daily	Angina, cardiac dysrhythmia, myocardial infarction, syncope
atenolol (generic) <sup>[4]</sup>	08/1981	expired	25 to 100 mg PO once daily	Anxiety, cardiac dysrhythmia, heart failure, drug withdrawal, migraine prevention, pre-eclampsia, syncope, tremor
bisoprolol (generic) <sup>[4]</sup>	07/1992	expired	5 to 20 mg PO once daily	Angina, atrial fibrillation, heart failure, migraine prevention
carvedilol (generic) <sup>[5]</sup>	09/1995	expired	6.25 to 25 mg PO twice daily	Angina, cardiac dysrhythmia, liver disease
carvedilol CR (Coreg CR™) <sup>[6]</sup>	10/2006	04/2010 12/2023	20 to 80 mg PO once daily	
labetalol (generic) <sup>[4]</sup>	08/1984	expired	100 to 600 mg PO twice daily	Angina, myocardial infarction, cardiac dysrhythmia, hypertension 2° drug overdose, pheochromocytoma, Raynaud's phenomenon
metoprolol (generic) <sup>[4]</sup>	08/1978	expired	25 to 100 mg PO twice daily	Aggressive behavior, angina, anxiety, myocardial infarction, cardiac dysrhythmia, migraine prevention, syncope, tremor
metoprolol succinate SR-24h (generic) <sup>[7]</sup>	01/1992	expired	50 to 400 mg PO once daily	
nadolol (generic) <sup>[4]</sup>	12/1979	expired	20 to 240 mg PO once daily	Myocardial infarction, aggressive behavior, anxiety, cardiac dysrhythmia, glaucoma, hyperthyroidism, tremor
nebivolol (Bystolic™) <sup>[2]</sup>	12/2007	06/2015 04/2020	5 to 40 mg PO once daily	None listed
pindolol (Visken®) <sup>[4]</sup>	09/1982	expired	5 to 30 mg PO twice daily	Myocardial infarction, aggressive behavior, anxiety, cardiac dysrhythmia, tremor, hyper-thyroidism, syncope
propranolol (Inderal®) <sup>[4]</sup>	11/1967	expired	20 to 120 mg PO twice daily	Aggressive behavior, anxiety, liver cirrhosis, heart failure, hypertension 2° drug overdose, thyroid storm, tremor, Tourette's syndrome
propranolol LA (Inderal® LA) <sup>[8]</sup>	04/1983	expired	60 to 240 mg PO once daily	
propranolol ERC (Innopran XL®) <sup>[9]</sup>	03/2003	12/2022	80 to 120 mg PO once daily	
timolol (Blocadren®) <sup>[4]</sup>	11/1981	expired	5 to 20 mg PO twice daily	Angina, anxiety, tremor, hyperthyroidism

<sup>a</sup> Date applies to approval date for the original brand name medication where there are now generics available.

<sup>b</sup> Based on patents listed in Orange Book as of 03/17/08.

<sup>c</sup> As listed in © 1974 - 2008 Thomson MICROMEDEX database or as referenced.

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