

## Indiana Medicaid Therapeutics Committee Therapeutic Class Review Summary

**Therapeutic class:**

Alpha-Beta blockers and Beta-blockers

**Overview:**

In general, all non-selective beta-blockers compete with catecholamines for binding at beta<sub>1</sub>- and beta<sub>2</sub>-receptor sites. However, selective beta-blockers bind to beta<sub>1</sub>-receptor sites at normal doses, but only bind to beta<sub>2</sub>-receptor sites at high doses. Blockage of beta<sub>1</sub>-receptors results in decreased heart rate, cardiac output, and systolic and diastolic blood pressure. Alternatively, blockage of beta<sub>2</sub>-receptors may induce bronchospasms. Other concerns associated with beta-receptor blockage include hypotension, bradycardia, masking of hypoglycemic effects, and thyrotoxicosis. Penbutolol and nebivolol are the only beta-blockers included in this review that are not available as generics.

Carvedilol and labetalol possess beta-blocking activity primarily; however, these agents also block alpha<sub>1</sub>-receptors in the vascular smooth muscle. Carvedilol has an increased ratio of beta to alpha<sub>1</sub> effects compared to that of labetalol. The result of alpha-beta blocking activity is vasodilation and decreased total peripheral resistance, which leads to a reduction in blood pressure without a significant effect on resting heart rate or cardiac output. Labetalol and carvedilol are indicated for hypertension; however, carvedilol also has indications for acute myocardial infarction, myocardial infarction prophylaxis, post myocardial infarction, cardiomyopathy, and heart failure. Carvedilol is now available in an extended-release formulation (Coreg CR™) with the same indications as immediate-release carvedilol.

All beta-blockers are indicated for hypertension. Bystolic, the newest beta-blocker available, is highly selective for beta<sub>1</sub>-receptors and is the most cardioselective of all the beta-blockers. Unlike other beta-blockers, Bystolic also decreases peripheral vascular resistance; however, available data supporting the superiority of Bystolic over alternative beta-blockers for treatment of hypertension are limited. Some agents are also indicated for angina, myocardial infarction, treatment of left ventricular dysfunction following myocardial infarction, migraines, and cardiac arrhythmias. Recent studies, such as Packer et al., evaluated carvedilol versus placebo in heart failure patients. The results showed that carvedilol, a nonselective alpha-beta blocker with antioxidant properties, reduced the rate of death in heart failure patients. Another study, MERIT-HF showed that metoprolol succinate (Toprol XL), a cardioselective beta-blocker, was beneficial for heart failure patients over placebo. The majority of the current data is limited to the comparison of carvedilol or metoprolol succinate with placebo. Until recently, the head-to-head studies comparing carvedilol and metoprolol were small-scale and yielded inconclusive results to determine a superior agent. However, at the recent European Society of Cardiology's Heart Failure 2003 meeting, results of the Carvedilol or Metoprolol European Trial (COMET) were released. COMET was a double-blind, randomized, parallel group study design that compared the effects of carvedilol or metoprolol tartrate (metoprolol tartrate does not have an indication for CHF) on the risk of death or hospitalizations in patients with congestive heart failure. COMET is the largest and longest study in CHF and the first head-to-head survival study comparing two beta-blocker agents. Results showed that patients with CHF treated with the non-selective alpha-beta blocker, carvedilol, had a significant survival benefit (p = 0.0017) as compared to those treated with metoprolol, a beta<sub>1</sub>-selective agent.

Generic Name	Brand Name	Manufacturer	Generic
<b>Alpha-Beta blockers</b>			
Carvedilol	Coreg <sup>®</sup> , Coreg CR™	GlaxoSmithKline	Y
Labetalol	Trandate <sup>®</sup> <i>(Brand product Normodyne discontinued)</i>	Schering Corp., Promethius	Y
<b>Nonselective Beta-blockers</b>			
Nadolol	Corgard <sup>®</sup>	Monarch Pharm Inc.	Y

Penbutolol	Levadol <sup>®</sup>	Schwarz Pharma Inc.	N
Pindolol	Visken <sup>®</sup>	Novartis	Y
Propranolol	Inderal <sup>®</sup> , Inderal <sup>®</sup> LA InnoPran XL <sup>™</sup>	Wyeth, Reliant Pharmaceuticals	Y
Sotalol	Betapace <sup>®</sup> , Betapace AF <sup>®</sup>	Berlex	Y
Timolol	Blocadren <sup>®</sup> (Brand product discontinued)	Merck and Co	Y
<b>Selective Beta-blockers</b>			
Acebutolol	Sectral <sup>®</sup>	ESP Pharma	Y
Atenolol	Tenormin <sup>®</sup>	AstraZeneca	Y
Betaxolol	Kerlone <sup>®</sup>	Sanofi-Synthelabo	Y
Bisoprolol fumarate	Zebeta <sup>®</sup>	Duramed	Y
Metoprolol tartrate	Lopressor <sup>®</sup>	Novartis	Y
Metoprolol succinate	Toprol XL <sup>®</sup>	AstraZeneca	Y
Nebivolol	Bystolic <sup>™</sup>	Forest Pharmaceuticals	N

**Summary:**

All beta-blockers are efficacious in the treatment of hypertension. Bystolic was recently approved and is the most cardioselective of all the beta-blockers; however, available data supporting its superiority over alternative agents for treatment of hypertension are limited. Some agents are also indicated for angina (propranolol, nadolol, atenolol, and metoprolol), arrhythmias (propranolol, sotalol and acebutolol), myocardial infarction (carvedilol, propranolol, timolol, atenolol, and metoprolol), treatment of left ventricular dysfunction following a myocardial infarction (carvedilol) and migraine (propranolol and timolol). The preferred drug list should be based upon FDA indications and generic availability.

\*Note: Esmolol, injectables and ophthalmic preparations were not discussed in this review.