

STEP THERAPY POLICY

POLICY: Beta Blocker Step Therapy Program

DATE REVIEWED: 04/29/2020

DRUGS AFFECTED:

Products available generically

- Sectral® (acebutolol capsules – Reddy Pharmaceuticals, generics)
- Tenormin® (atenolol tablets – AstraZeneca, generics)
- betaxolol tablets (generics)
- Zebeta® (bisoprolol tablets – Barr Pharmaceuticals, generics)
- Coreg® (carvedilol tablets – GlaxoSmithKline, generics)
- Coreg CR™ (carvedilol extended-release capsules – GlaxoSmithKline, generics)
- labetalol tablets (generics)
- Lopressor® (metoprolol tartrate tablets – Novartis, Mylan, generics)
- Toprol XL® (metoprolol succinate extended-release tablets – Aralez Pharmaceuticals, generics)
- Corgard® (nadolol tablets – King Pharmaceuticals, generics)
- pindolol tablets (generics)
- propranolol tablets (generics)
- Inderal® LA (propranolol extended-release capsules – Wyeth Ayerst, generics)
- Betapace® (sotalol tablets – Covis Pharma, generics)
- Betapace® AF (sotalol tablets – Covis Pharma, generics)
- timolol tablets (generics)
- Tenoretic® (atenolol/chlorthalidone tablets – AstraZeneca, generics)
- Ziac® (bisoprolol/hydrochlorothiazide tablets – Barr Laboratories, generics)
- Lopressor® HCT (metoprolol/hydrochlorothiazide tablets – Novartis, generics)
- Corzide® (nadolol/bendroflumethiazide tablets – King Pharmaceuticals, generics)
- propranolol/hydrochlorothiazide tablets (generics)

Products not available generically

- Dutoprol™ (metoprolol succinate extended-release tablets/hydrochlorothiazide – AstraZeneca)
- Bystolic™ (nebivolol tablets – Allergan)
- Byvalson™ (nebivolol and valsartan tablets – Allergan)
- Inderal XL® (propranolol extended-release capsules – Mist Pharmaceuticals)
- InnoPran XL® (propranolol extended-release capsules – Reliant)
- Kapsargo™ Sprinkle (metoprolol succinate capsules extended-release – Ohm Laboratories/Sun Pharmaceuticals)
- Metoprolol succinate/hydrochlorothiazide extended release tablets – Solubiomix

OVERVIEW

Beta-blockers can be classified into four pharmacologic subgroups based on their effect on beta and alpha receptors: cardioselective beta-blockers, nonselective beta-blockers, combined alpha-beta blockers, and beta-blockers with intrinsic sympathomimetic activity (ISA). Cardioselective beta-blockers are those agents that preferentially block beta-1 receptors over beta-2 receptors. Nonselective beta-blockers block both the beta-1 and beta-2 receptors. Based on mechanism of action, cardioselective beta-blockers may be safer than nonselective beta-blockers in patients with asthma, chronic obstructive pulmonary disease (COPD), peripheral arterial disease (PAD), and diabetes mellitus

who require beta-blocker therapy. However, cardioselectivity appears to be dose-dependent and at higher doses, cardioselective agents may lose their selectivity. The dose at which cardioselectivity is lost varies from patient to patient. Combined alpha-beta blockers nonselectively block beta receptors as well as alpha receptors. Beta-blockers with ISA act as partial beta-receptor agonists and therefore, resting heart rate, cardiac output, and peripheral blood flow are not as reduced.¹⁻³ Table 1 classifies the beta-blockers by subgroup.

Table 1. Beta-Blockers by Pharmacologic Subgroup.¹⁻⁵

Cardioselective beta-blockers	Nonselective beta-blockers	Combined alpha-beta blockers	Beta blockers with ISA
atenolol betaxolol bisoprolol metoprolol tartrate metoprolol succinate XL nebivolol ^{†*}	nadolol propranolol propranolol extended-release [‡] timolol	carvedilol carvedilol extended-release [°] labetalol	acebutolol penbutolol [^] pindolol

ISA – Intrinsic sympathomimetic activity; ⁺ May have vasodilatory properties; ^{*} In extensive metabolizers and at doses less than or equal to 10 mg nebivolol is preferentially beta₁ selective. In poor metabolizers and at higher doses, it is nonselective; [†] Available as Bystolic; [‡] Available as a generic and as InnoPran XL; [°] Available as Coreg CR; [^] Available as Levatol.

All of the beta-blockers included in this category are approved for the treatment of hypertension. Various reviews and guidelines address the role of beta blockers in hypertension.^{9,24-27} It is notable that sotalol (Betapace, Betapace AF) is not indicated for use in hypertension but instead is used for the management of arrhythmias.^{3-4,20} Specifically, Betapace/Betapace AF are indicated for the treatment of life-threatening ventricular arrhythmias as well as for the maintenance of normal sinus rhythm in patients with atrial fibrillation or flutter.²³ Betaxolol, bisoprolol, labetalol, Bystolic[™] (nebivolol tablets), Levatol[®] (penbutalol tablets), and pindolol are only indicated for the treatment of hypertension.^{3-4,20} The remaining beta-blockers (non-combination products) have at least one other indication. Such indications include angina pectoris, select arrhythmias, to treat and reduce cardiovascular (CV) mortality following a myocardial infarction (MI), to treat and reduce CV mortality in heart failure (HF), migraine prophylaxis, essential tremor, pheochromocytoma, and hypertrophic subaortic stenosis. All of the beta-blocker/diuretic combination products are indicated for the treatment of hypertension, although often not as initial therapy. Sotylize[™] (sotalol hydrochloride oral solution) is not included in this program as a generic is not available.^{3-4,20} Also, Hemangeol[™] (propranolol hydrochloride oral solution) is not included as this is indicated for the treatment of proliferating infantile hemangioma requiring systemic therapy.²¹

Carvedilol, metoprolol succinate extended-release (XL) and Coreg CR[™] (carvedilol extended-release capsules) are the only beta-blockers indicated in patients with HF.⁶⁻⁸ Metoprolol succinate XL is indicated for the treatment of stable, symptomatic (New York Heart Association [NYHA] class II or III) or mild-to-severe HF, respectively, of ischemic, hypertensive, or cardiomyopathic origin. Carvedilol and Coreg CR are indicated for the treatment of mild-to-severe HF of ischemic or cardiomyopathic origin.⁷⁻⁸ In combination with angiotensin converting enzyme (ACE) inhibitors, diuretics, and digitalis, both metoprolol succinate and carvedilol have been shown to decrease the rate of mortality and hospitalization. In addition, carvedilol and Coreg CR are indicated to reduce CV mortality in clinically stable patients who have survived the acute phase of an MI and have a left ventricular ejection fraction (LVEF) ≤ 40% with or without symptomatic HF. Byvalson[™] (nebivolol and valsartan tablets) is the only product that contains Bystolic, a beta blocker, plus an angiotensin II receptor blocker (ARB), valsartan; it is indicated for the treatment of hypertension.²²

Although there may be important pharmacologic differences among the various beta-blockers, they are all able to provide a similar degree of blood pressure lowering.¹ The Eight Joint National Committee (JNC 8) published evidence-based guidelines in 2014 regarding the management of high blood pressure in adults.⁹ In a general nonblack population, including patients with diabetes, initial antihypertensive therapy should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme (ACE) inhibitor, or an angiotensin receptor blocker (ARB). In the general black population, including patients with diabetes, initial antihypertensive therapy should include a thiazide-type diuretic or a CCB. Beta blockers were not recommended as initial antihypertensive therapy because in one study beta blocker therapy led to a higher rate in the primary composite outcome of CV death, MI or stroke compared to patients who were randomized to receive an ARB. Also, dual alpha/beta blocking agents (e.g., carvedilol), and vasodilating beta blockers (e.g., Bystolic™ [nebivolol tablets]) are not recommended as first-line therapy either. The 2017 guidelines regarding the management of high blood pressure in adults by the American College of Cardiology and the American Heart Association (AHA) also prominently mention the benefits with beta blockers in selected patients.²⁶

The benefits of beta-blocker therapy in the management of patients who have experienced an MI are well established. Also, data supports the substantial benefit of beta-blockers in addition to ACE inhibitor therapy in patients with transient or sustained postinfarction left ventricular (LV) dysfunction. In addition, the benefit of beta-blocker therapy as secondary prevention is recognized. The 2013 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines for the management of patients with ST-elevation MI relate the benefits of beta-blockers in patients post MI and do not differentiate between beta-blockers.¹¹ Guidelines published in 2007 from the ACC/AHA for the management of patients with unstable angina/non ST-elevation MI also state that beta-blockers should be administered to such patients in the absence of contraindications. The guidelines discuss the benefits of beta-blockers as a class, with no specific product recommended as first-line.¹² In 2012, the ACCF and the AHA, along with various other organizations, published guidelines for the diagnosis and management of patients with stable ischemic heart disease.¹⁰ Class I recommendations include that beta-blocker therapy should commence and be continued for 3 years in all patients with normal LV function after MI or acute coronary syndrome. Also, beta-blocker therapy should be used for all patients with LV systolic dysfunction (ejection fraction $\leq 40\%$) with HF or prior MI, unless use is contraindicated. Use should be limited to carvedilol, metoprolol succinate, or bisoprolol, which have demonstrated to reduce the risk of death.

In 2013, the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) published updated guidelines for the management of heart failure (HF).¹³ Three beta-blockers have been proven effective in reducing death in patients with chronic HF: bisoprolol,¹³⁻¹⁴ metoprolol succinate XL,^{13,15} and carvedilol.^{13,16-18} The guidelines state that the positive findings with these specific beta-blockers should not be considered indicative of a class effect.¹³ Bystolic demonstrated a modest reduction in the primary endpoint of all-cause mortality or CV hospitalization, but did not impact mortality alone in an elderly population that included patients with HF.^{13,19} Long-term therapy with beta-blockers can reduce HF symptoms, and improve the patient's clinical status. Beta-blockers also reduce the risk of death and the combined risk of death or hospitalization. The guidelines recommend use of one of the three beta-blockers proven to reduce mortality (i.e., bisoprolol, metoprolol succinate XL, and carvedilol) for all stable patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated, to reduce morbidity and mortality.¹³

Because there are several beta-blocker and beta-blocker combination products available as generics a step therapy program has been developed to encourage the use of a generic beta-blocker or generic beta-blocker combination product prior to the use of a brand name beta-blocker or brand name beta-blocker combination product.

POLICY STATEMENT

The program is comprised of two rules: 1) beta-blocker step therapy rule and 2) sotalol step therapy rule. Both programs have been developed to encourage use of one generic Step 1 product prior to the use of a Step 2 product. If the step therapy rule is not met for a Step 2 agent at the point of service, coverage will be determined by the step therapy criteria below. All approvals are provided for 12 months in duration.

Automation: Patients with a history of one Step 1 drug within the 130-day look-back period are excluded from step therapy.

Beta-Blocker Step Therapy Rule

Step 1A: generic beta-blockers (i.e., acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, carvedilol extended-release, labetalol, metoprolol tartrate, nadolol, pindolol, propranolol, timolol, metoprolol succinate extended-release, propranolol extended-release), and generic beta-blocker combination products (i.e., atenolol/chlorthalidone, bisoprolol/hydrochlorothiazide, metoprolol/hydrochlorothiazide, propranolol/hydrochlorothiazide, nadolol/bendroflumethiazide).

Step 2A: brand name beta-blockers (i.e., Bystolic, Sectral, Tenormin, Zebeta, Coreg, Coreg CR, Lopressor, Toprol XL, Corgard, Inderal LA, InnoPran XL, Inderal XL) and brand name beta-blocker combination products (i.e., Byvalson, Tenoretic, Ziac, Lopressor HCT, Corzide, Dutoprol, Metoprolol succinate/hydrochlorothiazide extended-release), Kaspargo Sprinkle.

Sotalol Step Therapy Rule

Step 1B: generic sotalol

Step 2B: brand name Betapace, Betapace AF

CRITERIA

Beta Blocker Step Therapy Rule

Exceptions for a Step 2A product can be made for those who have met one of the following criteria:

1. The patient has tried at least one Step 1A generic beta blocker or generic beta blocker combination product. Note: Sotalol products do not count toward this requirement.

Sotalol Step Therapy Rule

Exceptions for a Step 2B product can be made for those who have met one of the following criteria:

1. The patient has tried at least one Step 1B agent.
2. The strength of the requested Step 2B agent is not available generically.

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