

STEP THERAPY POLICY

POLICY: Beta Blocker Step Therapy Policy

Products available generically

- acebutolol capsules (generic only)
- Tenormin® (atenolol tablets – AstraZeneca, generic)
- betaxolol tablets (generic only)
- bisoprolol tablets (generic only)
- Coreg® (carvedilol tablets – Woodward, generic)
- Coreg CR™ (carvedilol extended-release capsules – Woodward, generic)
- labetalol tablets (generic only)
- labetalol 400 mg tablets (Brand) (Biocon Pharma)
- Lopressor® (metoprolol tartrate tablets – Novartis, Mylan, generic)
- Toprol XL® (metoprolol succinate extended-release tablets – Aralez, generic)
- Corgard® (nadolol tablets – King, generic)
- pindolol tablets (generic only)
- propranolol tablets (generic only)
- Inderal® LA (propranolol extended-release capsules – Wyeth Ayerst, generic)
- Betapace® (sotalol tablets – Covis, generic)
- Betapace® AF (sotalol tablets – Covis, generic)
- timolol tablets (generic only)
- Tenoretic® (atenolol/chlorthalidone tablets – AstraZeneca, generic)
- Ziac® (bisoprolol/hydrochlorothiazide tablets – Barr, generic)
- Lopressor® HCT (metoprolol/hydrochlorothiazide tablets – Novartis, generic)
- nadolol/bendroflumethiazide tablets (generic only)
- propranolol/hydrochlorothiazide tablets (generic only)

Products not available generically

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

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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, peripheral arterial disease, and diabetes mellitus who require beta-blocker therapy. However,

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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.¹⁻⁴

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 policy are approved for the **treatment of hypertension**. Various reviews and guidelines address the role of beta-blockers in hypertension.¹⁻⁸ Betaxolol, bisoprolol, labetalol, Bystolic™ (nebivolol tablets), Levatol® (penbutalol tablets), and pindolol are only indicated for the treatment of hypertension.¹⁻⁹ 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. It is notable that sotalol (Betapace, Betapace AF) is not indicated for use in hypertension but instead is used for the management of arrhythmias.^{3,4,10} 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.¹⁰ Sotylize™ (sotalol hydrochloride oral solution) is not included in this program as a generic is not available.^{3,4,11} Also, Hemangeol™ (propranolol hydrochloride oral solution) is not included as this is indicated for the treatment of proliferating infantile hemangioma requiring systemic therapy.¹²

Carvedilol, metoprolol succinate extended-release (XL) and Coreg CR™ (carvedilol extended-release capsules) are the only beta-blockers indicated in patients with HF¹⁴⁻¹⁶ with published data to support their use.¹⁷⁻²⁰ Metoprolol succinate XL is indicated to reduce the risk of cardiovascular mortality and HF hospitalization in patients with HF.¹⁴ Carvedilol and Coreg CR are indicated for the treatment of mild to severe HF of ischemic or cardiomyopathic origin.^{15,16} In combination with angiotensin converting enzyme 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 $\leq 40\%$ with or without symptomatic HF. Data are available with bisoprolol in patients with HF.²¹

Guidelines

Beta blockers are mentioned in a variety of guidelines. Main guidelines are briefly summarized.

- **Heart Failure:** In 2022, the American Heart Association (AHA), American College of Cardiology (ACC), and the Heart Failure Society of America published guidelines for the management of HF.²² The three beta-blockers proven to reduce mortality in patients with HF with reduced ejection fraction are bisoprolol, carvedilol, and sustained-release metoprolol succinate. Hospitalizations can also be reduced with these agents.
- **Hypertension:** The 2017 guidelines regarding the management of high blood pressure in adults by the ACC and the AHA prominently mention the benefits with beta blockers in selected patients.⁷
- **Chronic Coronary Disease:** Guidelines for the management of patients with chronic coronary disease (CCD) from the AHA and the ACC (2023) state that in adults with CCD and hypertension (systolic blood pressure ≥ 130 and/or diastolic blood pressure ≥ 80 mm Hg), in addition to nonpharmacological strategies, guideline-directed medication therapy with angiotensin-converting

enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), or beta blockers are recommended as first-line therapy for compelling indications (e.g., recent MI or angina), with additional antihypertensive medications (e.g., dihydropyridine calcium channel blockers [CCB], long-acting thiazide diuretics, and/or mineralocorticoid receptor antagonists) added as needed to optimize blood pressure control.¹³ In patients with CCD and left ventricular ejection fraction (LVEF) \leq 40% with or without previous MI, the use of beta-blocker therapy is recommended to reduce the risk of future major adverse CV events, including CV death. Also, in patients with CCD and LVEF $<$ 50%, the use of sustained release metoprolol succinate, carvedilol, or bisoprolol with titration to target doses is recommended in preference to other beta blockers.

POLICY STATEMENT

The program is comprised of two rules: 1) Beta-Blocker Step Therapy rule (Step A) and 2) Sotalol Step Therapy rule (Step B). This program has been developed to encourage the use of a Step 1A product prior to a Step 2A Product and a Step 1B Product prior to the use of a Step 2B Product. If the Step Therapy rule is not met for the Step 2A or Step 2B Product at the point of service, coverage will be determined by the Step Therapy criteria below. All approvals are provided for 1 year in duration.

Automation: For the Beta-Blocker Step Therapy Rule (Step A), a patient with a history of one Step 1A Product within the 130-day look-back period is excluded from Step Therapy. For the Sotalol Step Therapy Rule (Step B), a patient with a of one Step 1B Product within the 130-day look-back period is 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, Tenormin, Coreg, Coreg CR, Lopressor, Toprol XL, Corgard, Inderal LA, InnoPran XL, Inderal XL) and brand name beta-blocker combination products (i.e., Tenoretic, Ziac, Lopressor HCT, Dutoprol, Metoprolol succinate/hydrochlorothiazide extended-release), Kaspargo Sprinkle, Labetalol 400 mg tablet

Sotalol Step Therapy Rule

Step 1B: generic sotalol

Step 2B: brand name Betapace, Betapace AF

CRITERIA

Beta Blocker Step Therapy Rule

1. If the patient has tried one Step 1A Product, approve a Step 2A Product.

Note: Sotalol products do not count toward this requirement.

2. No other exceptions are recommended.

Sotalol Step Therapy Rule

1. If the patient has tried one Step 1B Product, approve a Step 2B Product.
2. If the strength of the requested Step 2B Product is not available generically, approve the Step 2B Product.
3. No other exceptions are recommended.

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