

STEP THERAPY POLICY

POLICY: Calcium Channel Blockers – Dihydropyridine Products Step Therapy Policy

- Adalat® CC (nifedipine extended-release tablets – Bayer, generics)
- Cardene® (nicardipine immediate-release capsules – generics only)
- Conjupri® (levamlodipine tablets – CSPC Ouyi Pharmaceutical)
- DynaCirc® (isradipine immediate-release capsules – generics only)
- Katerzia™ (amlodipine oral suspension – Silvergate Pharmaceuticals)
- Norvasc® (amlodipine tablets – Pfizer, generics)
- Plendil® (felodipine extended-release tablets – generics only)
- Prestalia® (perindopril arginine and amlodipine tablets – Symplmed)
- Procardia XL® (nifedipine extended-release tablets – Pfizer, generics)
- Procardia® (nifedipine immediate-release capsules – Pfizer, generics)
- Sular® (nisoldipine extended-release tablets – Shionogi, generics)

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OVERVIEW

All of the dihydropyridine (DHP) calcium channel blockers (CCBs), with the exception of immediate-release (IR) nifedipine and nimodipine, are indicated for the treatment of hypertension in adults.¹⁻¹⁴ Some of the DHP CCBs have unique indications:

- Agents that are indicated for the **management of chronic stable angina** include amlodipine, nicardipine IR, nifedipine IR, and nifedipine extended-release (ER) (Procardia XL formulation).
- Agents that are indicated for the **treatment of vasospastic angina** include amlodipine, nifedipine IR, and nifedipine ER (Procardia XL formulation).
- **Amlodipine** possess a unique indication in **patients with recently documented coronary artery disease by angiography and without heart failure (HF) or an ejection fraction < 40% to reduce the risk of hospitalization due to angina and to reduce the risk of a coronary revascularization procedure**. Amlodipine is indicated for use in children as young as 6 years of age.
- **Katerzia** may be used alone or in combination with other antihypertensive or an antianginal medications for the **treatment of hypertension** in adults and children ≥ 6 years of age and **coronary artery disease (CAD)** [chronic stable angina, vasospastic angina, and angiographically documented CAD in patients without heart failure or an ejection fraction < 40%].²⁴
- **Conjupri** is indicated for the **treatment of hypertension** in adults and pediatric patients ≥ 6 years of age to lower blood pressure.²⁵

Prestalia contains amlodipine and perindopril, an angiotensin converting enzyme inhibitor.⁶ The DHP CCB nimodipine is not discussed in this document since it is only indicated to improve neurological deficits associated with subarachnoid hemorrhage and is given every 4 hours for a 21-day period.¹³⁻¹⁴

Many of the available DHP CCBs can be dosed once daily (QD), which may be important in the treatment of hypertension to ensure adequate blood pressure control over a 24-hour period and in the treatment of angina to avoid fluctuations in blood pressure and heart rate. The only DHP CCBs that are not dosed QD are isradipine IR, dosed twice daily (BID), and nicardipine IR and nifedipine IR, both of which are dosed three to four times daily (TID to QID).

Hypertension

The DHP CCBs indicated in the treatment of hypertension have been found to be effective. These agents are useful for many reasons, such as the blood pressure response is less contingent on patient factors such as race and age, the agents are metabolically neutral and do not disturb glucose homeostasis; some agents have conferred cardiovascular benefit.¹⁵ In 2017 the American College of Cardiology (ACC), along with other nationally-recognized groups, published extensive guidelines regarding the management of high blood pressure in adults. CCBs are recommended among the choice of first-line agents as antihypertensive medications. Refer to the full guidelines for additional details.²³ The Eighth Report of the Joint National Committee (JNC 8) 2014 evidence based guideline for the management of high blood pressure in adults recommends CCBs as one of the initial choices of therapy in various scenarios.¹⁶ Currently, the only DHP CCB indicated for the treatment of hypertension in children is amlodipine (patients aged 6 to 17 years).¹ In 2017, the American Academy of Pediatrics published a clinical practice guideline regarding the management of high blood pressure in children and adolescents.¹⁷ Long-acting CCBs are among one of the first-line choices for patients initiating antihypertensive therapy.

Angina

In 2012, the Clinical Guidelines Committee of the American College of Physicians published guidelines for the management of stable ischemic heart disease.¹⁸ Long-acting nitrates or CCBs should be prescribed for relief of symptoms when beta-blockers are contraindicated or cause unacceptable adverse effects in patients with ischemic heart disease. Long-acting nitrates or CCBs in combination with beta blockers should be given for the relief of symptoms when initial treatment with beta-blockers is not successful in patients with stable ischemic heart disease. A particular CCB is not specified.

Heart Failure

Most of the clinical data available on the use of DHP CCBs in patients with HF are with amlodipine, followed by felodipine, although neither product is indicated for HF.¹⁹⁻²¹ The amlodipine prescribing information notes that amlodipine has been compared to placebo in several studies of 8 to 12 weeks duration in patients with New York Heart Association (NYHA) Class II/III HF (n = 697) and no evidence of worsening HF was noted.¹ The Prospective Randomized Amlodipine Evaluation (PRAISE) study (n = 1,153) is also detailed which involved use of amlodipine (5 to 10 mg) in patients with Class III/IV HF who were receiving other medications for HF (diuretics, digoxin, angiotensin converting enzyme [ACE] inhibitors).^{1,19} Amlodipine had no effect on the primary endpoint, which was the combined endpoint of all-cause mortality and cardiac morbidity. The primary endpoint occurred in 42% of patients given placebo vs. 39% in the amlodipine group after a median follow-up of 13.8 months.^{1,19} The PRAISE-2 trial is also mentioned in the amlodipine prescribing information which randomized patients with NYHA Class III (80%) or IV (20%) HF who had no clinical symptoms or objective evidence of underlying ischemic disease to receive placebo or amlodipine, in addition to other HF therapies. After a mean follow-up of 33 months, there was no difference between amlodipine and placebo in the primary endpoint of all-cause mortality.¹ The 2013 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guideline for the management of HF state that CCBs are not recommended as routine treatment in patients with HF.²² CCBs are included among the listed agents that may adversely impact the status of patients with current or prior symptoms of HF with reduced ejection fraction and should be avoided if possible, except amlodipine.

POLICY STATEMENT

This program has been developed to encourage the use of a Step 1 drug prior to the use of a Step 2 drug, for all agents except Prestalia. For Prestalia, this program requires the patient to try one Step 1 drug (a generic DHP CCB or a generic DHP CCB-combination product) and one angiotensin converting enzyme (ACE) inhibitor. If the Step Therapy rule is not met for a Step 2 drug 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: A patient with a history of one Step 1 drug within the 130-day look-back period is excluded from Step Therapy, except for Prestalia. For Prestalia, a patient with a history of one Step 1 drug and one brand or generic ACE inhibitor within the 130-day look-back period is excluded from Step Therapy.

Step 1: Afeditab CR, felodipine ER, nicardipine IR, nifedipine ER, nifedipine IR, nifedipine XL, Nifedical XL, Nifediac CC, isradipine IR, amlodipine, amlodipine/benazepril, nisoldipine ER, amlodipine/atorvastatin

Step 2: Adalat CC, Conjugri, Katerzia, Norvasc, Prestalia, Procardia, Procardia XL, Sular

CRITERIA

1. For all agents except Prestalia, if the patient has tried one Step 1 drug, approve a Step 2 drug.
2. For Prestalia, approve if the patient has tried one Step 1 drug AND one angiotensin converting enzyme inhibitor.
Note: Examples of angiotensin converting enzyme inhibitors include perindopril arginine, enalapril, lisinopril, benazepril.
3. For Katerzia, approve if the patient cannot or has difficulty swallowing tablets or capsules.

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