STEP THERAPY POLICY

POLICY: Calcium Channel Blockers – Dihydropyridine Products Step Therapy Policy

- Cardene® (nicardipine immediate-release capsules – generic only)
- Conjupri® (levamlodipine tablets – CSPC Ouyi)
- DynaCirc® (isradipine immediate-release capsules – generic only)
- Katerzia™ (amlodipine oral suspension – Azurity)
- Norvasc® (amlodipine tablets – Pfizer, generic)
- Levamlodipine tablets – Xspire/CSPC Ouyi (authorized generic)
- Norliqva® (amlodipine oral solution – CMP)
- Plendil® (felodipine extended-release tablets – generic only)
- Prestalia® (perindopril arginine and amlodipine tablets – Adhera)
- Procardia XL® (nifedipine extended-release tablets – Pfizer, generic)
- Procardia® (nifedipine immediate-release capsules – Pfizer, generic)
- Sular® (nisoldipine extended-release tablets – Shionogi, generic)

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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**.[1-14,9] Some of the DHB 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 adults and pediatric patients ≥ 6 years of age.
- **Conjupri** is indicated for the **treatment of hypertension** in adults and pediatric patients ≥ 6 years of age to lower blood pressure.[24] An authorized generic is available.[27]
- **Katerzia** may be used alone or in combination with other antihypertensive or 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%].[25]
- **Norliqva** may be used alone or in combination with other antihypertensive or antianginal medications for the **treatment of hypertension** in adults and children ≥ 6 years of age and **CAD** [chronic stable angina, vasospastic angina, and angiographically documented CAD in patients without heart failure or an ejection fraction < 40%].[26]

Prestalia contains amlodipine and perindopril, an angiotensin converting enzyme (ACE) 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 that 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, and 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 the first-line choices for patients initiating antihypertensive therapy.

Angina

In 2023, the **American Heart Association** and the **American College of Cardiology**, along with other national organizations, published guidelines regarding the management of patients with chronic coronary disease.[18] Either a calcium channel blocker or beta blocker is recommended as first-line antianginal therapy. In adults with chronic coronary disease and hypertension (systolic blood pressure ≥ 130 and/or diastolic blood pressure BP ≥ 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. In patients with chronic coronary disease and angina, antianginal therapy with either a beta blocker, CCB, or long-acting nitrate is recommended for relief of angina or equivalent symptoms. In such patients who remain symptomatic after initial treatment, addition of a second antianginal agent from a different therapeutic class (beta blockers, CCBs, long-acting nitrates) is recommended for relief of angina or equivalent symptoms.

Heart Failure (HF)

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 with 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, 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 2022 **American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/Heart Failure Society of**

America guideline for the management of HF states that DHP CCBs are not recommended for patients with heart failure and a reduced ejection fraction; no distinct benefits are noted.[22] DHP CCBs may be used for the treatment of hypertension in patients who have elevated blood pressure despite optimization of guideline-directed medication therapy. Among the DHP CCBs, amlodipine and felodipine are thought to have less myocardial depressant activity and may be more favorable agents.[22]

POLICY STATEMENT

This program has been developed to encourage the use of a Step 1 Product prior to the use of a Step 2 Product, for all agents except Prestalia. For Prestalia, this program requires the patient to try one Step 1 Product (a generic dihydropyridine-calcium channel blocker [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 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: A patient with a history of one Step 1 Product within the 130-day look-back period is excluded from Step Therapy, except for Prestalia. For Prestalia, a patient with a of one Step 1 Product and one brand or generic ACE inhibitor within the 130-day look-back period is excluded from Step Therapy.

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

Step 2: Conjupri, Katerzia, Levamlodipine (authorized generic), Norliqva, Norvasc, Prestalia, Procardia, Procardia XL, Sular

CRITERIA

1. For all agents except Prestalia, if the patient has tried one Step 1 Product, approve a Step 2 Product.

2. For Prestalia, if the patient has tried one Step 1 Product AND one angiotensin converting enzyme inhibitor, approve Prestalia.
Note: Examples of angiotensin converting enzyme inhibitors include perindopril, enalapril, lisinopril, benazepril.

3. If the patient cannot swallow or has difficulty swallowing tablets or capsules, approve Katerzia or Norliqva.

4. No other exceptions are recommended.

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