

## **Therapeutic Class Overview Calcium-Channel Blocking Agents (Dihydropyridines)**

### **Therapeutic Class Overview/Summary:**

Calcium-channel blockers (CCBs) have multiple roles in treating cardiovascular disease. The movement of calcium ions is essential for the function of all types of muscle, including cardiac muscle and vascular smooth muscle. For both cardiac and smooth muscle, the flow of calcium ions into the muscle cells through specific channels allows muscle contraction to occur. When this flow is reduced, the result is a weakening of muscle contraction and relaxation of muscle tissue.<sup>1-2</sup> Calcium-channel blockade has certain effects that are specific to cardiac function. Coronary vascular smooth muscle relaxes when calcium channels are blocked, which increases the flow of oxygenated blood into the myocardium and lowers coronary vascular resistance.<sup>3,4</sup> In addition, CCBs decrease peripheral vascular resistance by relaxing arteriolar smooth muscle. Both coronary and systemic vasodilation serve to reduce cardiac workload.<sup>5</sup> There are two classes of CCBs dihydropyridines, which are similar in chemical structure, and non-dihydropyridines, which are a structurally miscellaneous group.

Dihydropyridines are more potent vasodilators than non-dihydropyridines due to greater selectivity for vascular smooth muscle. They have a lesser effect, or even no effect, upon cardiac muscle contractility or conduction.<sup>1-6-26</sup> One of the non-dihydropyridines, diltiazem is a potent coronary vasodilator, but is only a mild arterial vasodilator. Although it decreases atrioventricular (AV) node conduction, diltiazem does not have negative inotropic properties.<sup>27-32</sup> The other non-dihydropyridine, verapamil, dilates coronary and peripheral arteries. It also slows conduction through the AV node, and has negative inotropic and chronotropic effects.<sup>33-37</sup> A complete list of indications for the calcium channel blockers and combination products can be found in Table 1a and 1b.<sup>6-38</sup>

**Table 1a. Current Medications Available in the Therapeutic Class (Dihydropyridines)<sup>6-26</sup>**

<b>Generic (Trade Name)</b>	<b>Food and Drug Administration-Approved Indications</b>	<b>Dosage Form/Strength</b>	<b>Generic Availability</b>
<b>Single Entity Agents</b>			
Amlodipine (Norvasc®*)	Chronic stable angina; variant (vasospastic) angina; hypertension; to reduce the risk of hospitalization for angina and coronary revascularization procedures in patients with CAD;	Tablet: 2.5 mg 5 mg 10 mg	✓
Clevidipine (Cleviprex®)	Hypertension	IV Emulsion: 0.5 mg/mL	-
Felodipine ER*	Hypertension	ER Tablet (SR 24-hour): 2.5 mg 5 mg 10 mg	✓
Isradipine*	Hypertension	Capsule: 2.5 mg 5 mg	✓
Nicardipine* (Cardene IV®)	Hypertension	Capsule: 20 mg 30 mg  IV Solution: 2.5 mg/mL 5 mg/mL* 10 mg/mL*	✓

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Nifedipine* (Procardia®*)	Chronic stable angina (capsule); hypertension	Capsule: 10 mg 20 mg	✓
Nifedipine ER (Adalat CC®*, Afeditab CR®†, Nifediac CC®†, Nifedical XL®†, Procardia XL®*)	chronic stable angina without evidence of vasospasm; hypertension	ER Tablet (SR-24 hour): 30 mg 60 mg 90 mg  Osmotic Release capsule (SR-24 hour): 30 mg 60 mg 90 mg	✓
Nimodipine* (Nymalize®)	Subarachnoid hemorrhage, from ruptured intracranial berry aneurysms (Hunt and Hess Grades I-V)	Capsule: 30 mg  Oral Solution: 60 mg/20 mL	✓
Nisoldipine* (Sular®*)	Hypertension	ER Tablet (SR-24 hour): 8.5 mg 17 mg 20 mg 25.5 mg 30 mg 34 mg 40 mg	✓
<b>Two Agent Combination Products</b>			
Amlodipine/atorvastatin (Caduet®*)	Hyperlipidemia, hypertension	Tablet: 2.5/10 mg 2.5/20 mg 2.5/40 mg 5/10 mg 5/20 mg 5/40 mg 5/80 mg 10/10 mg 10/20 mg 10/40 mg 10/80 mg	✓
Amlodipine/benazepril (Lotrel®*)	Hypertension	Capsule: 2.5/10 mg 5/10 mg 5/40 mg 10/20 mg 10/40 mg	✓
Amlodipine/perindopril (Prexalia®)	Hypertension	Tablet: 2.5/3.5 mg 5/7 mg 10/14 mg	-

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Amlodipine/olmesartan (Azor®)	Hypertension	Tablet: 5/20 mg 5/40 mg 10/20 mg 10/40 mg	-
Amlodipine/valsartan (Exforge®*)	Hypertension	Tablet: 5/160 mg 5/320 mg 10/160 mg 10/320 mg	✓
Amlodipine/telmisartan (Twynsta®*)	Hypertension	Tablet: 5/40 mg 5/80 mg 10/40 mg 10/80 mg	✓
<b>Three Agent Combination Products</b>			
Amlodipine/olmesartan/hydrochlorothiazide (Tribenzor®)	Hypertension	Tablet: 5/20/12.5 mg 5/40/12.5 mg 5/40/25 mg 10/40/12.5 mg 10/40/25 mg	-
Amlodipine/valsartan/hydrochlorothiazide (Exforge HCT®*)	Hypertension	Tablet: 5/160/12.5 mg 5/160/25 mg 10/160/12.5 mg 10/160/25 mg 10/320/12.5 mg 10/320/25 mg	✓

\*Generic available in at least one dosage form or strength.

†Branded-generic

**Table 1b. Current Medications Available in the Therapeutic Class (Non-Dihydropyridines)<sup>27-38</sup>**

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
<b>Single Entity Agents</b>			
Diltiazem* (Cardizem®*)	Angina due to coronary artery spasm (tablet); chronic stable angina (tablet); rapid conversion to sinus rhythm of paroxysmal supraventricular tachycardias (injection); temporary control of rapid ventricular rate in atrial flutter or atrial fibrillation (injection)	IV solution: 25 mg/5 mL 50 mg/10 mL 125 mg/25 mL 125 mg/125 mL*  Tablet: 30 mg 60 mg 90 mg 120 mg	✓
Diltiazem ER* (Cardizem CD®*, Cardizem LA®*, Cartia XT®†, Dilt-XR®†, Matzim LA®†, Tiazac®*, Taztia XT®†)	Angina due to coronary artery spasm; chronic stable angina	ER bead capsule (SR 24-hour): 120 mg 180 mg 240 mg	✓

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
		300 mg 360 mg 420 mg  ER bead tablet (SR 24-hour): 120 mg 180 mg 240 mg 300 mg 360 mg 420 mg  ER capsule (SR 12-hour): 60 mg 90 mg 120 mg  ER capsule (SR 24-hour): 120 mg 180 mg 240 mg	
Verapamil* (Calan®*)	Chronic stable angina (tablet), unstable angina (tablet), vasospastic angina (tablet), ventricular rate control in chronic atrial fibrillation and/or atrial flutter in association with digitalis; prophylaxis of repetitive paroxysmal supraventricular tachycardia; temporary control of rapid ventricular rate in atrial flutter or atrial fibrillation (injection); hypertension	IV solution: 2.5 mg/mL  Tablet: 40 mg 80 mg 120 mg	✓
Verapamil ER* (Calan SR®*, Verelan®*, Verelan PM®)	Hypertension	CR Tablet: 120 mg 180 mg 240 mg  ER capsule (SR 24-hour): 100 mg 120 mg 180 mg 200 mg 240 mg 300 mg 360 mg	✓
<b>Two Agent Combination Products</b>			
Verapamil/trandolapril ER	Hypertension	CR tablet:	✓

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
(Tarka <sup>®*</sup> )		180/2 mg 240/1 mg 240/2 mg 240/4 mg	

\*Generic available in at least one dosage form or strength.

†Branded-generic

### Evidence-based Medicine

- Safety and efficacy has been established for a number of agents for various indications.
- Both dihydropyridines and non-dihydropyridines have been evaluated in and approved by the FDA for: angina, cardiovascular outcomes, hypertension and other miscellaneous diagnoses.<sup>39-160</sup>

### Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - In general the calcium channel blockers have been extensively studied in clinical trials for their FDA-approved diagnose.<sup>39-160</sup>
  - For angina, guidelines recommend long-acting CCBs as first line, or in some cases after failure with a  $\beta$ -blocker. In Vasospastic angina,  $\beta$ -blockers should be avoided and CCBs are among first-line recommended agents.<sup>161-167</sup>
  - CCBs are generally not offered to reduce cardiovascular risk after a myocardial infarction.<sup>168</sup>
  - When used in patients with heart failure, nondihydropyridine calcium channel blockers may be harmful in patients with low left ventricular ejection fraction (LVEF). Patients with hypertension and symptomatic left ventricular dysfunction with left ventricular dilation and low LVEF may consider a dihydropyridine calcium channel blocker or other antihypertensive medication if blood pressure remains >130/80 mmHg. CCBs can be used in heart failure patients who have preserved LVEF who have atrial fibrillation requiring ventricular rate control and intolerance to  $\beta$ -blockers (consider diltiazem or verapamil), symptom-limiting angina, or hypertension.<sup>169-171</sup>
  - For the treatment of hypertension, CCBs are considered first line along with many other antihypertensive classes. Addition of a CCB to other antihypertensives may be needed to achieve therapeutic blood pressure levels.<sup>172-175</sup>
- Other Key Facts:
  - There are a number of generic calcium channel blockers currently marketed. Amlodipine, felodipine extended release (ER), isradipine, nicardipine, nifedipine, nifedipine ER, nimodipine, nisoldipine, diltiazem and verapamil are all available as a generic product in at least one dosage form or strength. In addition, generic combination products include amlodipine/atorvastatin, amlodipine/benazepril, amlodipine/valsartan, amlodipine/telmisartan, amlodipine/valsartan/hydrochlorothiazide and verapamil/trandolapril ER.

### References

Refer to the therapeutic class review for a complete list of references.