INTRODUCTION

- Approximately 121.5 million American adults are living with some form of cardiovascular disease (consisting of coronary heart disease, heart failure, stroke, and hypertension) according to the American Heart Association Heart (AHA) Disease and Stroke Statistics 2019 update. Cardiovascular disease accounts for nearly 840,678 deaths in the United States (US) annually (Benjamin et al 2019).
- 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. In addition, calcium channel blocking agents (also called calcium channel blockers) decrease peripheral vascular resistance by relaxing arteriolar smooth muscle. Both coronary and systemic vasodilation serve to reduce cardiac workload (Kannam et al 2019, Dobesh PP 2017, Michel T 2011).
- 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 (Micromedex 2.0 2019, Kannam et al 2019).
- The calcium channel blocking agents include dihydropyridines, which are similar in chemical structure, and non-dihydropyridines, which are a structurally heterogeneous group. Although they have different binding sites on the L-type calcium channel, both block the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The non-dihydropyridines also block the T-type calcium channel in the atrioventricular (AV) node (Micromedex 2.0 2019, Kannam et al 2019, Dobesh PP 2017, Michel T 2011, Saseen 2017).
- Dihydropyridines are more potent vasodilators than non-dihydropyridines due to greater selectivity for vascular smooth muscle. They have little effect on cardiac muscle contractility or conduction (Micromedex 2.0 2019, Kannam et al 2019).
  - All available dihydropyridine calcium channel blocking agents can be used in the treatment of hypertension, with the exception of nimodipine and immediate release nifedipine capsules. Although not a first-line treatment in all hypertensive patients, the dihydropyridines are generally effective but differ somewhat in other properties and effects.
  - Amlodipine, oral nicardipine, and long-acting nifedipine are effective treatment options for chronic stable angina. Short-acting agents, such as short-acting nifedipine, should be avoided due to increased cardiovascular and mortality risks in some patients as well as significant adverse effects, such as reflex tachycardia. Amlodipine is also indicated to reduce the risk of hospitalization due to angina and to reduce the risk of a coronary revascularization procedure in patients with recently documented coronary artery disease (CAD).
  - Amlodipine is the only calcium channel blocker that is Food and Drug Administration (FDA)-approved in combination with a nonsteroidal anti-inflammatory drug (NSAID). Consensi (amlodipine/celecoxib) was FDA-approved on May 31, 2018 for the treatment of hypertension and osteoarthritis.
- The non-dihydropyridine calcium channel blocking agents include diltiazem and verapamil and both agents are available in a variety of modified-release delivery systems that alter their pharmacokinetic properties, including onset and duration of action (Micromedex 2.0 2019). Non-dihydropyridines dilate the arteries somewhat less than dihydropyridines, but they also reduce heart rate and contractility (Micromedex 2.0 2019, Kannam et al 2019, Weber et al 2014).
  - The non-dihydropyridine calcium channel blocking agents are indicated for use in the treatment of angina, arrhythmias, and hypertension. Diltiazem is a potent coronary vasodilator but is only a mild arterial vasodilator. Although it decreases AV node conduction, diltiazem does not have negative inotropic properties. Verapamil dilates coronary and peripheral arteries. It also slows conduction through the AV node and has negative inotropic and chronotropic effects (Micromedex 2.0, 2019).
  - Guidelines stipulate that a non-dihydropyridine calcium channel blocker may be prescribed in certain patients, often with co-morbid indications. Non-dihydropyridine calcium-channel blocking agents are not recommended for the routine treatment of heart failure because of their negative inotropic action and risk of worsening heart failure (Yancy et al 2013, Yancy et al 2016, Yancy et al 2017). Caution is also advised in elderly patients. Guidelines generally reserve non-dihydropyridine calcium channel blockers for patients with high risk cardiovascular diseases and
Calcium channel blockers are also included in various combination products (eg, amlodipine-benazepril); however, these combination agents are not included in this review.

Since there are several branded agents that contain the same generic component, the remaining tables in the review are organized by generic name. This review encompasses all dosage forms and strengths with the exception of injectable indications and formulations used primarily in an institutional setting.

**Medispan Therapeutic Class: Calcium Channel Blockers**

**Table 1. Medications Included Within Class Review**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Generic Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dihydropyridines</strong></td>
<td></td>
</tr>
<tr>
<td>Adalat CC (nifedipine extended-release)</td>
<td>✓</td>
</tr>
<tr>
<td>Consensi (amlodipine/celecoxib)</td>
<td>-</td>
</tr>
<tr>
<td>Felodipine extended-release</td>
<td>✓</td>
</tr>
<tr>
<td>Isradipine</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Katerzia (amlodipine suspension)</strong></td>
<td>✓</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>✓</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>✓</td>
</tr>
<tr>
<td>Nisoldipine extended-release</td>
<td>✓</td>
</tr>
<tr>
<td>Norvasc (amlodipine)</td>
<td>✓</td>
</tr>
<tr>
<td>Nymalize (nimodipine)</td>
<td>-</td>
</tr>
<tr>
<td>Procardia (nifedipine)</td>
<td>✓</td>
</tr>
<tr>
<td>Procardia XL (nifedipine extended-release)</td>
<td>✓</td>
</tr>
<tr>
<td>Sular (nisoldipine extended-release)</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Non-dihydropyridines</strong></td>
<td></td>
</tr>
<tr>
<td>Calan (verapamil) tablet</td>
<td>✓</td>
</tr>
<tr>
<td>Calan SR (verapamil extended-release) tablet</td>
<td>✓</td>
</tr>
<tr>
<td>Cardizem (diltiazem) tablet</td>
<td>✓</td>
</tr>
<tr>
<td>Cardizem CD* (diltiazem extended-release) capsule</td>
<td>✓</td>
</tr>
<tr>
<td>Cardizem LA† (diltiazem extended-release) tablet</td>
<td>✓</td>
</tr>
<tr>
<td>Dilacor XR‡ (diltiazem extended-release) capsule</td>
<td>✓</td>
</tr>
<tr>
<td>Tiazac§ (diltiazem extended-release) capsule</td>
<td>✓</td>
</tr>
<tr>
<td>Verelan (verapamil sustained-release) capsule</td>
<td>✓</td>
</tr>
<tr>
<td>Verelan PM (verapamil extended-release) capsule</td>
<td>✓</td>
</tr>
</tbody>
</table>

*Cartia XT is a branded generic of Cardizem CD.
†Matzim LA is the branded generic of Cardizem LA.
‡Dilacor XR is no longer manufactured, but included in this review because its branded generic, DILT-XR, is still on the market.
§Taztia XT and Diltzac are branded generics of Tiazac.

**INDICATIONS**

**Table 2. FDA-Approved Indications – Dihydropyridines**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Amlodipine</th>
<th>Consensi (amlodipine/celecoxib)</th>
<th>Felodipine</th>
<th>Isradipine</th>
<th>Nicardipine</th>
<th>Nifedipine</th>
<th>Nimodipine</th>
<th>Nisoldipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina Pectoris</td>
<td>✓</td>
<td>-</td>
<td>-</td>
<td>✓†</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Treatment of chronic stable angina

*Cartia XT is a branded generic of Cardizem CD.
†Matzim LA is the branded generic of Cardizem LA.
‡Dilacor XR is no longer manufactured, but included in this review because its branded generic, DILT-XR, is still on the market.
§Taztia XT and Diltzac are branded generics of Tiazac.
### Table 3. Food and Drug Administration Approved Indications – Non-Dihydropyridines

<table>
<thead>
<tr>
<th>Indication</th>
<th>Diltiazem</th>
<th>Verapamil</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Angina Pectoris</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina due to coronary artery spasm or vasospastic angina</td>
<td>✓ (tablet [Cardizem], extended-release capsule [Cardizem CD])</td>
<td>✓ (Calan)</td>
</tr>
<tr>
<td>Chronic stable angina</td>
<td>✓</td>
<td>✓ (Calan)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>-</td>
<td>✓ (Calan)</td>
</tr>
<tr>
<td><strong>Arrhythmias</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Alone or in combination with other antianginal agents.
†Alone or in combination with beta blockers.
‡Confirmed or suspected vasospastic angina. May be used alone or in combination with other antianginal agents.
§Vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm.
║Alone or in combination with other antihypertensive agents.
¶Alone or in combination with thiazide-type diuretics.

Control of ventricular rate at rest and during stress in patients with chronic atrial flutter and/or atrial fibrillation in association with digitalis

Prophylaxis of repetitive paroxysmal supraventricular tachycardia

Hypertension

Hypertension to lower blood pressure which reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.

Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

**CLINICAL EFFICACY SUMMARY**

**Dihydropyridines**

- Clinical trials have demonstrated the efficacy of these agents for their respective indications.

- Amlodipine oral suspension has a pharmacokinetic profile comparable to the tablet formulations, and received FDA approval based on these pharmacokinetic parameters and the efficacy of amlodipine tablet (*Katerzia prescribing information 2019*).

- In a crossover study for the treatment of angina, amlodipine and felodipine have been shown to be more effective than placebo, though no significant difference between the 2 active treatment groups was observed (*Koenig 1997)*.


- In-class comparisons for the treatment of hypertension have found better compliance and a higher response rate with amlodipine compared to felodipine, though van der Krogt and colleagues found similar decreases in overall systolic and diastolic blood pressures between groups (*Sheehy et al 2000, Van der Krogt et al 1996)*.


*May be used alone or in combination with other antihypertensive agents.

In the ALLHAT study, ACE inhibitors had a 51% higher rate (relative risk [RR], 1.51; 95% confidence interval [CI], 1.22 to 1.86) of stroke in patients of African or Caribbean descent (Black) when used as initial therapy compared to calcium channel blockers. ACE inhibitors were also less effective in reducing blood pressure in Black patients compared to a calcium channel blocker (Rahman et al 2012, Black et al 2008, ALLHAT 2002).

- An unpublished phase III randomized controlled trial compared amlodipine/celecoxib (Consensi) with its individual components and matching placebo in 152 patients with hypertension (Smith et al, 2018). After 2 weeks of treatment, the primary endpoint of change in mean daytime ambulatory systolic blood pressure was noninferior with amlodipine/celecoxib vs amlodipine (-10.6 vs -8.8 mmHg; p < 0.001), and the secondary endpoint of mean 24-hour diastolic blood pressure was superior with amlodipine/celecoxib vs amlodipine (-7.1 vs -4.8 mmHg; p = 0.38).
- A Cochrane review determined that calcium channel blockers do not have a role in the management of patients with acute ischemic stroke (Zhang et al 2019).

**Non-dihydropyridines**

- The non-dihydropyridine calcium channel blockers are indicated to treat hypertension and angina, in addition to slowing ventricular rate in patients with atrial fibrillation/atrial flutter. Clinical trials demonstrate the efficacy of these agents for their respective indications.
- For the treatment of angina, diltiazem and verapamil have been shown to be effective in improving exercise tolerance and reducing heart rate, angina frequency and nitroglycerin use (De Rosa et al 1998, Chugh et al 2001, van Kesteren et al 1998, Frishman et al 1999).
  - A direct comparison between diltiazem and verapamil found no significant differences between the agents in exercise tolerance; however, resting heart rate, angina frequency and nitroglycerin use were all significantly lower in the diltiazem group (De Rosa et al 1998).
- Both diltiazem and verapamil have shown efficacy in the treatment of hypertension, but comparisons with other classes of medications have not consistently demonstrated “superiority” of either agent (Wright et al 2004, Rosei et al 1997).
  - Wright and colleagues compared diltiazem and amlodipine in African American patients with hypertension and demonstrated significantly greater reductions in diastolic blood pressure during the first 4 hours after awakening in addition to greater reductions in heart rate with diltiazem; however, mean 24-hour systolic blood pressure reductions were significantly greater with amlodipine (Wright et al 2004).
- Studies evaluating the efficacy of the non-dihydropyridine calcium channel blockers for various cardiovascular outcomes generally demonstrated no significant difference between verapamil or diltiazem compared to other agents including beta blockers and diuretics (Hansson et al 2000, Pepine et al 2003, Mancia et al 2007, Bangalore et al 2008, Black et al 2003).

### CLINICAL GUIDELINES

- There are several national and international evidence-based antihypertensive guidelines that provide recommendations regarding the use of calcium channel blocking agents. Most recommend that the selection of an antihypertensive agent be based on compelling indications for use:
  - Most guidelines recommend a thiazide-type diuretic, an ACE inhibitor, an ARB, or a calcium channel blocker as first-line therapy (Go et al 2014, James et al 2014, Williams et al 2018, Weber et al 2014, Carey et al 2018). The 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guideline generally recommends that combination therapy include an ACE inhibitor or ARB with a calcium channel blocker and/or a thiazide-type diuretic (Williams et al 2018).
  - In Black hypertensive patients, thiazide-type diuretics or calcium channel blockers are recommended specifically as first-line therapy (James et al 2014, Williams et al 2018, Weber et al 2014).
  - In patients with chronic kidney disease, calcium channel blockers are generally recommended after ACE inhibitors or ARBs (KDIGO 2012, Go et al 2014, Williams et al 2018, Weber et al 2014).
  - Consensus guidelines recommend calcium channel blockers as an option in pregnant patients with severe hypertension to prevent stroke; nifedipine is one of the only dihydropyridines tested in these patients (Bushnell et al 2014, Williams et al 2018).
  - A long-acting dihydropyridine calcium channel blocker may be added to a basic hypertensive regimen, particularly after a beta blocker and ACE inhibitor, in hypertensive patients with CAD and stable angina (Rosendorff et al 2015).
A non-dihydropyridine calcium channel blocker may be prescribed for hypertensive patients with CAD who have an intolerance or contraindication to a beta blocker; however, a combination of a beta blocker and a non-dihydropyridine calcium channel blocker may increase the risk of bradyarrhythmias and heart failure (Rosendorff et al 2015).

Non-dihydropyridine calcium-channel blocking agents are not recommended for the routine treatment of heart failure because of their negative inotropic action and risk of worsening heart failure (Yancy et al 2016, Yancy et al 2017).

The 2018 ESC/ESH guidelines recommend calcium channel blockers, ACE inhibitors, and ARBs over beta-blockers or diuretics in patients with left ventricular (LV) hypertrophy (Williams et al 2018). However, in general, calcium channel blocking agents are not recommended for the routine treatment of heart failure (Ponikowski et al 2016, Yancy et al 2013, Yancy et al 2016, Yancy et al 2017), although, some guidelines agree that some dihydropyridine calcium channel blockers may be used in certain co-morbid conditions if the patient has preserved LV function (Ponikowski et al 2016).

In November 2017, the American College of Cardiology (ACC)/AHA released the 2017 Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults. For initial first-line therapy for stage 1 hypertension, they list thiazide diuretics, calcium channel blockers, and ACE inhibitors or ARBs. In African American adults with hypertension but without heart failure or CKD, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or calcium channel blocker. Two or more antihypertensive medications are recommended to achieve a BP target of < 130/80 mm Hg in most adults, especially in African American adults, with hypertension (Whelton et al 2017).

In August 2017, the American Academy of Pediatrics (AAP) published practice guidelines for screening and management of high blood pressure in children and adolescents. In hypertensive children and adolescents who have failed lifestyle modifications (particularly those who have LV hypertrophy on echocardiography, symptomatic hypertension, or stage 2 hypertension without a clearly modifiable factor [eg, obesity]), the guidelines recommend initiating pharmacologic treatment with an ACE inhibitor, ARB, long-acting calcium channel blocker, or thiazide diuretic (Flynn et al 2017).

- For the treatment of chronic angina, beta blockers are recommended as initial therapy; however, long-acting calcium channel blocking agents may be used if beta blockers are contraindicated or if additional therapy is required (Fihn et al 2012, Fihn et al 2014, Knuuti et al 2019, O’Gara et al 2013, Montalescot et al 2013). Beta blockers and calcium channel blockers have similar clinical outcomes, but beta blockers may have fewer adverse events in patients with stable angina. Long-acting calcium channel blockers may be used in combination with beta blockers when beta blocker monotherapy is unsuccessful (Montalescot et al 2013, Amsterdam et al 2014). Other guidelines recommend long-acting calcium channel blockers and nitrates as a treatment option for coronary artery spasm. For vasospastic (Prinzmetal) angina, guidelines recommend calcium channel blockers alone or in combination with nitrates (Amsterdam et al 2014).

- For the treatment of aneurysmal SAH, oral nimodipine is recommended to reduce poor outcome related to SAH (Connolly et al 2012, Diringer et al 2011).

- For patients with ventricular tachycardias, non-dihydropyridine calcium channel blockers have a limited role and administration of these agents can lead to further cardiovascular decompensation (Al-Khatib et al 2017). Verapamil is effective in treating idiopathic interfascicular reentrant left ventricular tachycardia.
• Dihydropyridine calcium channel blockers can produce negative inotropic effects and exacerbate heart failure and as a result, patients with heart failure should be monitored carefully.
• Caution should be exercised when using dihydropyridine calcium channel blockers in patients with impaired hepatic function or reduced hepatic blood flow because these agents are extensively metabolized by the liver.
• In general, monitoring should be performed for blood pressure (with initiation and titration), heart rate and anginal pain. Patients should also be monitored for signs and symptoms of edema.
• Consensi (amlodipine/celecoxib) carries a boxed warning for the risk of serious cardiovascular and gastrointestinal (GI) events. Consensi is contraindicated in the setting of coronary artery bypass surgery. The celecoxib component is associated with serious GI adverse events, such as bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal.

Non-dihydropyridine
• Diltiazem is contraindicated in patients with i) acute myocardial infarction and pulmonary congestion documented by X-ray on admission, ii) hypersensitivity to the drug, iii) hypotension (< 90 mm Hg systolic), iv) second or third degree AV block except in the presence of a functioning ventricular pacemaker, and v) sick sinus syndrome except in the presence of a functioning ventricular pacemaker. Verapamil is contraindicated in patients with i) atrial fibrillation or flutter and an accessory bypass tract (Wolff-Parkinson-White, Lown-Ganong-Levine syndromes), ii) hypersensitivity to the drug, iii) hypotension (< 90 mm Hg systolic), iv) second or third degree AV block except in the presence of a functioning ventricular pacemaker, v) severe left ventricular dysfunction, and vi) sick sinus syndrome except in the presence of a functioning ventricular pacemaker.
• The precautions for diltiazem include the following: may have an additive effect on heart rate with concomitant use of beta blockers or digitalis; dermatologic reactions leading to erythema multiforme and/or exfoliative dermatitis have been reported; increased risk of toxicity with hepatic and/or renal impairment; hypotension; impaired ventricular function and worsening congestive heart failure have also been reported. The precautions for verapamil include the following: concomitant use of a beta blocker in patients with any degree of ventricular dysfunction and concomitant use of quinidine in patients with hypotrophic cardiomyopathy should be avoided; congestive heart failure may occur; elevated liver enzymes, particularly serum transaminase levels, have been reported; first-degree AV block, marked, or progression to second- or third-degree block may occur; hepatic function impairment may occur; sinus bradycardia, pulmonary edema, severe hypotension, second-degree AV block, sinus arrest, and death have been reported in patients with hypertrophic cardiomyopathy; hypotension and/or dizziness may occur; pulmonary edema may occur.
• In general, patients taking non-dihydropyridine calcium channel blocking agents should have their blood pressure monitored weekly during the initial period of titration. Heart rate and anginal pain should also be monitored. Patients should have their liver function monitored periodically. Electrocardiogram (ECG) should be monitored for PR interval prolongation in patients with impaired renal or hepatic function using verapamil. If the medication is being used for arrhythmia, then ECG and reduction in signs and symptoms should be monitored.
• The common adverse effects of diltiazem include bradycardia, cough, dizziness, fatigue, headache and peripheral edema. The common adverse effects of verapamil include constipation, dizziness, edema, headache, hypotension, influenza-like symptoms, pharyngitis, and sinusitis.

(Facts and Comparisons 2019, Micromedex 2.0 2019)

**DOSSING AND ADMINISTRATION**

**Table 4. Dosing and Administration - Dihydropyridine**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Available Formulations</th>
<th>Usual Recommended Frequency</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>Oral tablets</td>
<td>Angina pectoris (chronic stable and vasospastic): Tablet, suspension: maintenance, 5 to 10 mg once daily; maximum, 10 mg once daily</td>
<td>Doses in excess of 5 mg daily have not been studied in pediatric patients. In general, wait 7 to 14 days between titration steps. Titrate more rapidly, however, if clinically</td>
</tr>
<tr>
<td></td>
<td>Oral suspension</td>
<td>CAD:</td>
<td></td>
</tr>
</tbody>
</table>

(Facts and Comparisons 2019, Micromedex 2.0 2019)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Available Formulations</th>
<th>Usual Recommended Frequency</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Tablet, <strong>suspension</strong>: maintenance, 5 to 10 mg once daily; maximum, 10 mg once daily</td>
<td>warranted, provided the patient is assessed frequently.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Hypertension:</strong> Tablet, <strong>suspension</strong>: initial, 5 mg once daily; maintenance, 5 to 10 mg once daily; maximum, 10 mg once daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Hypertension in children 6 to 17 years of age:</strong> Tablet, <strong>suspension</strong>: initial, 2.5 mg once daily; maintenance, 2.5 to 5 mg once daily; maximum, 5 mg once daily</td>
<td></td>
</tr>
<tr>
<td>Consensi</td>
<td>Oral tablets</td>
<td>Hypertension and osteoarthritis: Initial, 5 mg/200 mg once daily (or 2.5 mg/200 mg in small, elderly, or frail patients or those with hepatic impairment); titrate to 5 mg/200 mg or 10 mg/200 mg once daily as needed.</td>
<td></td>
</tr>
<tr>
<td>(amlodipine/celecoxib)</td>
<td></td>
<td>The lowest effective dose of celecoxib for the shortest duration should be used. Consensi may be substituted for its individual components.</td>
<td></td>
</tr>
<tr>
<td>Felodipine</td>
<td>Oral extended-release tablets</td>
<td>Hypertension: Extended-release tablet: initial, 5 mg once daily; maintenance, 2.5 to 10 mg once daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose adjustments should occur generally at intervals of not less than 2 weeks. Should be swallowed whole and not crushed or chewed; take without food or with a light meal.</td>
<td></td>
</tr>
<tr>
<td>Isradipine</td>
<td>Oral capsules</td>
<td>Hypertension: Capsule: initial, 2.5 mg twice daily; maximum, 20 mg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose adjustments should occur in increments of 5 mg/day at 2 to 4 week intervals.</td>
<td></td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Oral capsules</td>
<td><strong>Angina pectoris (chronic stable):</strong> Capsule: initial, 20 mg 3 times daily; maintenance, 20 to 40 mg 3 times daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypertension: Capsule: initial, 20 mg 3 times daily; maintenance, 20 to 40 mg 3 times daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allow at least 3 days before increasing the dose to ensure achievement of steady state plasma drug concentrations (capsule formulation).</td>
<td></td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Immediate-release capsules</td>
<td><strong>Angina pectoris (chronic stable):</strong> Capsule: initial, 10 mg 3 times daily; maintenance, 10 to 20 mg 3 times daily; maximum, 180 mg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Extended-release tablets</td>
<td>Titration should proceed over a 7- to 14-day period.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Extended-release tablets should be swallowed whole, not bitten or divided and should be taken on an...</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Available Formulations</td>
<td>Usual Recommended Frequency</td>
<td>Comments</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>empty stomach; co-administration with grapefruit juice should be avoided.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Extended-release tablet: initial, 30 or 60 mg once daily; maximum, 90 mg/day</td>
<td>Angina pectoris (vasospastic): Capsule: initial, 10 mg 3 times daily; maintenance, 20 to 30 mg 3 to 4 times daily; maximum, 180 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Angina pectoris (vasospastic): Extended-release tablet: initial, 30 or 60 mg once daily; maximum, 90 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypertension: Extended-release tablet: initial, 30 or 60 mg once daily; maintenance, 30 to 90 mg once daily; maximum, 120 mg/day</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>Oral capsules</td>
<td>Subarachnoid hemorrhage: Capsule: 60 mg every 4 hours for 21 consecutive days</td>
<td>Dosing should be started within 96 hours of subarachnoid hemorrhage. Capsules should be swallowed whole with a little liquid and oral solution should only be administered enterally, preferably not less than 1 hour before or 2 hours after meals; grapefruit juice should be avoided; capsules should not be administered intravenously or by other parenteral routes.</td>
</tr>
<tr>
<td></td>
<td>Oral solution</td>
<td>Oral solution: 20 mL (60 mg) every 4 hours for 21 consecutive days</td>
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<td></td>
<td></td>
<td>Extended-release tablets</td>
<td>Hypertension: Extended-release tablet: initial, 20 mg once daily; maintenance, 20 to 40 mg/day; maximum, 60 mg/day</td>
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<td>Extended-release tablet (Sular and its generics): initial, 17 mg once daily; maintenance, 17 to 34 mg once daily; maximum, 34 mg once daily</td>
<td>Dose adjustments should occur at intervals of not less than 1 week. Extended-release tablets should be swallowed whole, not bitten, divided or crushed; should be taken on an empty stomach (1 hour before or 2 hours after a meal); grapefruit products should be avoided; administration with a high fat meal can lead to excessive</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>Extended-release tablets</td>
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<tr>
<td>Drug</td>
<td>Available Formulations</td>
<td>Usual Recommended Frequency</td>
<td>Comments</td>
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<tr>
<td>Diltiazem</td>
<td>Extended-release capsules</td>
<td>Angina pectoris (chronic stable): Extended-release capsule: initial, 120 or 180 mg once daily; maintenance, 180 to 540 mg once daily; maximum, 540 mg once daily</td>
<td>Tablet formulation should be taken before meals and at bedtime. Tiazac (extended-release) capsule formulation may also be administered by opening the capsule and sprinkling the capsule contents on a spoonful of applesauce; the applesauce should be swallowed immediately without chewing and followed with a glass of cool water to ensure complete swallowing of the capsule contents. Cardizem LA (extended-release) tablets should be swallowed whole and not chewed or crushed.</td>
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<tr>
<td></td>
<td>Extended-release tablets</td>
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<td></td>
<td>Tablets</td>
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<td></td>
<td></td>
<td>Extended-release tablet: initial, 180 mg once daily; maximum, 360 mg once daily</td>
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<td></td>
<td></td>
<td>Tablet: initial, 30 mg 4 times daily; maintenance, 180 to 360 mg/day (divided in 3 to 4 doses)</td>
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<td>Angina pectoris (due to coronary artery spasm):</td>
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<td></td>
<td>Extended-release capsule (Cardizem CD): initial, 120 or 180 mg once daily; maintenance, adjust dosage to each patient’s needs up to 480 mg once daily</td>
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<tr>
<td></td>
<td></td>
<td>Tablet: initial, 30 mg 4 times daily; maintenance, 180 to 360 mg/day (divided in 3 to 4 doses)</td>
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<td></td>
<td></td>
<td>Hypertension:</td>
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<td></td>
<td></td>
<td>Extended-release capsule: initial, 120 to 240 mg once daily; maintenance, 120 to 540 mg once daily; maximum, 540 mg once daily</td>
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<td></td>
<td></td>
<td>Extended-release tablet: initial, 180 to 240 mg once daily, although some patients may respond to lower doses; maximum, 540 mg once daily</td>
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<tr>
<td>Verapamil</td>
<td>Extended-release capsules</td>
<td>Angina pectoris (chronic stable, unstable, and vasospastic):</td>
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<td></td>
<td>Extended-release tablets</td>
<td>Tablet: maintenance, 80 to 120 mg 3 times daily</td>
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<td></td>
<td>Sustained-release capsules</td>
<td>Arrhythmias:</td>
<td></td>
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<td></td>
<td>Tablets</td>
<td>Tablet: maintenance, 240 to 320 mg/day, divided in 3 to 4 doses; maximum, 480 mg/day</td>
<td>Calan 80 mg tablets are scored and can be divided into halves to provide a 40 mg dose. Calan SR should be administered with food and if needed the caplets can be divided in half without compromising the sustained-release properties of the drug.</td>
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<tr>
<td>Drug</td>
<td>Available Formulations</td>
<td>Usual Recommended Frequency</td>
<td>Comments</td>
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<tr>
<td>Hypertension:</td>
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<td>Sustained-release capsule: initial, 120 to 240 mg once daily; maintenance, 180 mg to 480 mg/day; maximum, 480 mg/day</td>
<td>Verelan and Verelan PM capsules should not be crushed or chewed and they may be administered by opening the capsule and sprinkling the capsule contents on a spoonful of applesauce; the applesauce should be swallowed immediately without chewing and followed with a glass of cool water to ensure complete swallowing of the capsule contents.</td>
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<td>Extended-release capsule: initial, 100 mg to 200 mg once daily at bedtime; maintenance, 200 mg to 400 mg once daily; maximum, 400 mg/day</td>
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<td>Extended-release tablet: initial, 120 to 180 mg in the morning; maintenance, 180 to 480 mg/day in 1 to 2 divided doses, maximum, 480 mg/day</td>
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<td></td>
<td>Tablet: initial, 80 mg 3 times daily; maintenance, 360 to 480 mg/day divided (3 to 4 times daily); maximum, 480 mg/day</td>
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</table>

See the current prescribing information for full details.

**CONCLUSION**

- All of the dihydropyridines, with the exception of nimodipine, are approved for the treatment of hypertension. Amlodipine, nicardipine, and nifedipine are also indicated for the treatment of angina. Additionally, amlodipine reduces the risk of hospitalization due to angina and reduces the risk of coronary revascularization procedures in patients with recently documented CAD. Consensi, a combination of amlodipine and celecoxib, was recently FDA-approved for the treatment of patients with hypertension and osteoarthritis. Nimodipine improves the neurological outcome of patients with an SAH by reducing the incidence and severity of ischemic deficits in patients with ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition (ie, Hunt and Hess Grades I-V).

- Numerous clinical trials have shown that the dihydropyridines can effectively lower systolic and diastolic blood pressure when administered alone or in combination with other agents. In trials comparing combination therapy to monotherapy, the more aggressive treatment regimens lowered blood pressure to a greater extent than the less intensive treatment regimens. Some comparative trials have demonstrated slight differences in blood pressure effects among the various dihydropyridines; however, the clinical significance of these differences remains to be established.

- The dihydropyridines have been shown to favorably affect cardiovascular morbidity and mortality, and several studies have demonstrated comparable efficacy with beta blockers, diuretics, ACE inhibitors, and ARBs in select diseases. However, the ALLHAT study demonstrated that patients of African or Caribbean descent (Black) had a lower rate of stroke when therapy was initiated with a calcium channel blocker compared to an ACE inhibitor.

- There is insufficient evidence to support that one dihydropyridine calcium channel blocker is safer or more efficacious than another, although most clinical trial experience has been with amlodipine and nifedipine.

- The non-dihydropyridine calcium channel blocking agents are approved for the treatment of angina, arrhythmias, and hypertension. Diltiazem and verapamil are available in a variety of modified-release delivery systems that alter their pharmacokinetic properties, including onset and duration of action.

- Clinical trials demonstrate that diltiazem and verapamil can effectively treat angina and improve blood pressure. Both agents have been shown to reduce mortality and cardiovascular event rates compared to placebo. Evidence suggests that there is no overall difference between diltiazem and verapamil compared to other antihypertensive agents (beta blockers, diuretics) in reducing cardiovascular events and mortality in patients with hypertension. There is insufficient
• Dihydropyridine

For the treatment of chronic angina, beta blockers are recommended as initial therapy; however, long-acting calcium-channel blocking agents may be used if beta blockers are contraindicated or if additional therapy is required. Beta blockers and calcium channel blockers have similar clinical outcomes, but beta blockers may have fewer adverse events in patients with stable angina. Long-acting calcium channel blockers may be used in combination with beta blockers when beta blocker monotherapy is unsuccessful. Long-acting calcium-channel blocking agents are also recommended in patients with variant angina and for patients with coronary artery spasm(s), known as vasospastic angina, with or without nitrates.

• Treatment options for atrial fibrillation include ventricular rate control or drug therapy to maintain sinus rhythm. The AFFIRM, RACE and HOT CAFE trials demonstrated similar outcomes with rate control compared to rhythm control strategies. Beta blockers or non-dihydropyridine calcium channel blockers are recommended for patients with persistent, paroxysmal, or permanent atrial fibrillation; however, in patients with decompensated heart failure or pre-excitation and atrial fibrillation, non-dihydropyridine calcium channel blockers should not be administered. Propafenone or flecainide (“pill-in-the-pocket”) in combination with a beta blocker or non-dihydropyridine calcium channel blocker are options to terminate atrial fibrillation outside of a hospital for select patients. Non-dihydropyridine calcium channel blockers may also be prescribed as monotherapy or in combination with other treatment in patients with atrial fibrillation and co-morbid hypertrophic cardiomyopathy, certain acute coronary syndrome patients, or chronic obstructive pulmonary disease. In cases of ventricular and supraventricular arrhythmias, intravenous non-dihydropyridine calcium channel blockers are recommended. Oral non-dihydropyridine calcium channel blockers may be used for the chronic management of patients with symptomatic supraventricular tachycardia without ventricular excitation.

Caution is advised with use in elderly patients with systolic heart failure; non-dihydropyridine calcium channel blockers have the potential to promote fluid retention and/or exacerbate heart failure.

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• Irasadipine prescribing information. Actavis Pharma, Inc. Parsippany, NJ. June 2017.


Messeri FH, Oparil S, Feng Z. Comparison of efficacy and side effects of combination therapy of angiotensin-converting enzyme inhibitor (benazepril) with calcium antagonist (either nifedipine or amlopidine) vs high-dose calcium antagonist monotherapy for systemic hypertension. Am J Cardiol. 2000 Dec 1;86:1182-7.


to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.


Non-dihydropyridine


• CARDIZEM prescribing information. Valeant Pharmaceuticals North America, LLC; Bridgewater, NJ. November 2016.


• DILT-XR prescribing information. Apotex, Inc; Weston, FL. July 2012.

• VERELAN PM prescribing information. Recro Gainesville LLC. Gainesville, GA. October 2019.

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