

# CALCIUM CHANNEL BLOCKING DRUGS

The calcium channel blocking drugs (CCBs) are a heterogeneous group of compounds that are classified according to chemical structure: diphenylalkylamines (verapamil), benzothiazepines (diltiazem), dihydropyridines (nifedipine, amlodipine, felodipine, nimodipine), and diphenylpiperazines (flunarizine).

## ACTION: (TABLES Ia and Ib)

All CCBs inhibit calcium flow through voltage-operated L-type slow calcium channels in cell membranes. These agents are differentiated according to their relative effects on vascular smooth muscle (vasodilation), myocardium (contractility), or conduction and pacemaker tissues (automaticity). Compared with verapamil and diltiazem, the dihydropyridines are more selective for vascular sites than for myocardial sites, and thus, exhibit greater vaso-dilatory effects with minimal electrophysiologic (AV and SA node conduction) or negative inotropic effects. In contrast, verapamil predominantly affects nonvascular smooth muscle and thus demonstrates greater negative chronotropic, dromotropic (affecting conductivity) and inotropic cardiac effects. Therefore, side effects associated with verapamil are typically nonvascular in nature (e.g. constipation and other gastrointestinal effects). Diltiazem exhibits intermediate vasoselectivity. Nimodipine and flunarizine are more selective for cerebral arteries than systemic arteries.

Clinically, decreased afterload and reflex increases in heart rate usually compensate for CCB-induced negative inotropic effects, except in patients with impaired left ventricular function (e.g. CHF). Calcium channel blocker therapy may adversely affect long-term clinical outcome and survival in patients with CHF. With the dihydropyridines, reflex tachycardia usually diminishes with chronic use. The newer "second generation" dihydropyridines (e.g. amlodipine, felodipine) are more vasoselective with lower negative inotropic effects. As well, reflex tachycardia is less prominent since fluctuations in plasma levels are less pronounced with these agents.

**TABLE Ia: VASCULAR AND CARDIAC EFFECTS**

	Verapamil	Diltiazem	Nifedipine	Flunarizine
Peripheral vasodilation	+	+	++	0
Heart rate	Increase/decrease	None/decrease	Increase	0
Depression of SA/AV nodal conduction	++	+	Minimal	0
Negative inotropic effect	Moderate	Mild	None/slight	0
Coronary artery dilation	+	+	++	0
Cardiac output	Increase/decrease	None/increase	Increase	0
Cerebrovascular dilation			+	+++

**TABLE Ib: VASCULAR AND CARDIAC EFFECTS**

	Amlodipine	Felodipine (extended release)	Nimodipine
Peripheral vasodilation	++	++	0/+
Heart rate	0	None/slight increase	0
Depression of SA/AV nodal conduction	0	0	0
Negative inotropic effect	None/slight	0	0
Coronary artery dilation	+	+	0
Cardiac output	Increase	Increase	0
Cerebrovascular dilation			+++

+ = some effect

++, +++ = significant, marked effect

0 = no significant effect

## PHARMACOKINETICS: (TABLES IIa and IIb)

The CCBs are generally well absorbed following oral administration. However, all the CCBs (except for amlodipine) undergo extensive first-pass metabolism, which significantly reduces bioavailability. All CCBs are highly bound to plasma proteins. Most CCBs (except for amlodipine) are inherently short acting due to a rapid elimination half-life. Frequent administration is required; extended release formulations allow for less frequent dosing. Plasma half-lives of most of the CCBs are increased in the **elderly** and in patients with liver disease. Bioavailability is increased by grapefruit juice (see Interactions).

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**TABLE IIa: PHARMACOKINETICS (ORAL)**

	Verapamil	Diltiazem	Nifedipine	Flunarizine
Bioavailability (%)	20-35	40	45-75	NA
Decreased absorption with food	Slight/none (tabs)	No	No	NA
Protein binding (%)	90	80	>90	99
Active metabolite	Yes	Yes	No	NA
Main elimination route	Hepatic	Hepatic	Hepatic	Hepatic
Elimination half-life (h)	5-12 8-12 (SR)	4-6 5-7 (SR) 5-8 (CD) 4-10 (ER)	2-5 10 (SR)	19 days
Hepatic impairment t 1/2 (h)	Increased* (14-16)	Increased*	Increased* (7)	NA
Renal impairment t 1/2 (h)	Unchanged	Unchanged	Unchanged	NA
Elderly t 1/2 (h)	Slight increase*	Increased* (10)	Increased* (7-9)	Unchanged
Onset of action (minutes)	30 240-300 (CER)	30-60 120-180 (SR, CD)	20	NA
Duration of action (h)	6-8 24 (SR, CER)	4-8 12 (SR) 24 (CD, ER)	4-8 12 (PA) 24 (XL)	NA
Usual dosing frequency	TID-QID BID (SR) Daily (SR cap, CER)	TID-QID BID (SR) Daily (CD, ER)	TID-QID BID (PA) Daily (XL)	Daily

**TABLE IIb: PHARMACOKINETICS (ORAL)**

	Amlodipine	Felodipine (extended release)	Nimodipine
Bioavailability(%)	60-65	10-25	3-28
Decreased absorption with food	No	No	Yes
Protein binding(%)	>95	>99	98
Active metabolite	No	No	No
Main elimination route	Hepatic	Hepatic	Hepatic
Elimination half-life (h)	35-45	11-16	2-6
Hepatic Impairment t 1/2 (h)	Increased* (60)	Increased* (2-3 times)	Increased*
Renal impairment t 1/2 (h)	Unchanged	Unchanged	Increased*
Elderly t 1/2 (h)	Increased* (48-69)	Increased* (24-29)	May increase*
Onset of action (minutes)	NA	120-300	NA
Duration of action (h)	24	24	4-5
Usual dosing frequency	Daily	Daily	Q4H x 21 days

\*Dosage reduction and careful titration of dosage required.  
NA Not available.

**USES AND EFFICACY: (TABLES III, IV)**

**Hypertension:** The potent arterial vasodilatory effects of CCBs make them highly effective in the treatment of hypertension. In addition, their natriuretic action (except possibly with felodipine) contributes to their long-term efficacy. These agents lower blood pressure without causing significant chronic reflex tachycardia and without interfering with autonomic baroreflex cardiovascular responses. Renally, CCBs decrease renovascular resistance and increase glomerular filtration rate.

CCBs are effective in any age group (including children) and in White or Black populations with low plasma renin levels, as monotherapy or combined with other antihypertensive agents including diuretics, beta blockers or ACE inhibitors. As monotherapy, the CCBs that have been used to treat hypertension appear to be equally effective, controlling blood pressure in approximately 60-80% of patients with mild to moderate hypertension. The newer CCBs have not been shown to be more effective than older agents.

CCBs do not adversely affect plasma electrolytes, or lipids, making them favourable therapy in hypertensive patients with coexistent gout, chronic renal failure, or hyperlipidemia. They are also safe in patients with coexistent chronic obstructive pulmonary disease, peripheral atherosclerotic disease, or Raynaud's phenomenon. CCBs may provide additional benefits in hypertensive patients with concomitant angina pectoris, supraventricular tachycardia (verapamil) or peripheral vascular disease (nifedipine). Like other antihypertensive agents, CCBs induce regression of left ventricular hypertrophy, and like ACE inhibitors, CCBs do not adversely affect quality of life.

CCBs are not recommended as first-line antihypertensive therapy due to a lack of convincing evidence that they decrease hypertension-associated cardiovascular morbidity or mortality. Data from large, long-term studies (INSIGHT and NORDIL) examining the effect of first-line CCBs at reducing cardiovascular complications associated with hypertension suggests they are as effective as beta blockers or diuretics. However, when specific outcomes (e.g. heart failure, stroke risk) are compared, the studies show conflicting or inconclusive results. High withdrawal rates in CCB-treated patients, problems with study design, and the influence of concurrent antihypertensives are examples of problems associated with these trials. Meta-analysis data (includes INSIGHT and NORDIL trials) suggests an increased incidence of myocardial infarction and congestive heart failure in those who receive long-acting CCBs as first-line antihypertensive therapy compared to those who received other agents. Short-acting dihydropyridines, especially nifedipine, should be avoided due to increased risk of myocardial infarction observed in case-control studies. Pooled analysis of studies suggests an increased risk of mortality or reinfarction in patients with coronary artery disease or previous myocardial infarction who are using short-acting dihydropyridines.

In hypertensive patients with diabetic nephropathy, diltiazem is the CCB (but not the drug) of choice (reduces proteinuria) (also see Angiotensin Converting Enzyme Inhibitors monograph). Nifedipine should not be used in these patients as it may increase proteinuria. Data from studies suggesting patients with **diabetes mellitus** may be at increased risk for cardiovascular complications with CCB therapy should be interpreted cautiously because of methodological problems. Larger randomized trials suggest that CCB therapy is safe in diabetics with hypertension (many patients in these trials were also treated with ACE inhibitors, beta blockers, and/or hydrochlorothiazide).

**Angina:** In chronic stable (exercise-induced) angina and unstable angina, CCBs are second- or third-line agents (after beta blockers and oral nitrates). They improve exercise tolerance and reduce the frequency and severity of anginal attacks and silent ischemic episodes. CCBs are the drugs of choice for Prinzmetal's variant angina. The newer CCBs have not demonstrated superiority over older CCBs.

In chronic stable angina, CCBs appear to be as effective as beta blockers. In unstable angina, diltiazem and verapamil, but not nifedipine have been shown to be comparable in efficacy to beta blockers. CCBs are not effective when used alone for the treatment of unstable angina. Verapamil, diltiazem and nifedipine are generally comparable in efficacy in Prinzmetal's and chronic stable angina. Thus, selection of a CCB may be based on differences in the pharmacologic profile (e.g. slowing of heart rate with verapamil or diltiazem, or marked vasodilation with nifedipine) and patient tolerance. It has been recommended that short-acting nifedipine be avoided due to reflex tachycardia and concerns about long-term effects.

**Prevention therapy in coronary artery disease:**

**Prevention of post-myocardial infarction morbidity and mortality (secondary prevention):** Large trials failed to demonstrate any overall benefit with either nifedipine or diltiazem in the secondary prevention of myocardial infarction. Furthermore, these trials showed a higher frequency of secondary cardiac events with diltiazem in patients with left ventricular dysfunction. Although verapamil has been shown to reduce death or reinfarction rates in patients without heart failure (but not in those with heart failure), the magnitude of this reduction is relatively small compared with that with beta blockers or platelet inhibitors (approximately 15% vs 25 to 30% with beta blockers and acetylsalicylic acid). However, much of these data were gathered before thrombolytics and angioplasty became standard treatment for these patients. To study whether CCBs may have a secondary prevention role in thrombolytic-treated myocardial infarction patients, Boden et al compared diltiazem 300 mg vs placebo once daily in a six-month, double-blind study. Diltiazem was not found to significantly reduce cardiac death, non-fatal reinfarction, or refractory ischemia. However, high-risk patients were excluded from the study, which resulted in a very low overall death rate. Another small pilot study found a significant reduction in death, reinfarction, and heart failure when verapamil was combined with an ACE inhibitor (trandolapril) in diuretic-treated post-myocardial infarction patients with heart failure. An ongoing trial will further study the role of combination ACE inhibitors and verapamil in post infarction patients with heart failure.

**Antiatherosclerotic effects:** In vitro and animal data suggest that some of the CCBs (amlodipine, diltiazem, felodipine, nifedipine, isradipine, verapamil) may slow the development and progression of atherosclerosis. Preliminary investigations suggest an effect on new or minimal lesions but no significant effect on advanced atherosclerotic lesions. Data from a three-year study comparing the effect of isradipine vs hydrochlorothiazide (MIDAS) on atherosclerotic progression in carotid arteries showed no difference between the two treatment groups. In another three-year study comparing amlodipine to placebo (PREVENT), there was no difference between the two groups in angiographic progression of coronary atherosclerosis. However, secondary findings suggest reduced carotid atherosclerosis, decreased rates of unstable angina, and reduced need for revascularization in amlodipine-treated patients with existing coronary heart disease who were also receiving beta blockers, nitrates, and/or lipid-lowering agents.

**Congestive heart failure:** CCBs are generally avoided in patients with CHF because of the risk of increased cardiovascular morbidity and mortality. This is probably related to their intrinsic negative inotropic effects and neurohormonal activating properties; ACE inhibitors are preferred in these patients. Limited evidence suggests that second generation dihydropyridines (e.g. amlodipine and felodipine) have no overall influence on survival in patients with CHF indicating that they may be safe for those who need additional treatment for angina or hypertension. There are no data to support the use of CCBs as primary treatment for CHF. CCBs should also be used cautiously in patients with sick sinus syndrome, or AV block.

**Arrhythmias:** Verapamil and diltiazem are useful for treatment of certain supraventricular arrhythmias. They should not be used in patients with atrial fibrillation or flutter associated with accessory bypass tracts (see individual monographs).

**Subarachnoid hemorrhage:** Controlled studies suggest that administration of nimodipine for 2 to 3 weeks, combined with early surgical repair of ruptured aneurysms provides some protection against delayed ischemic deterioration, permanent neurological damage, cerebral infarction, and death (see Nimodipine monograph).

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**TABLE III: CLINICAL USES:**

	Verapamil	Diltiazem	Nifedipine	Amlodipine	Felodipine
Angina: Stable	+	+	+	+	
Prinzmetal's	+	+	+	+	
Unstable	+	+	+		
Hypertension	+	+	+	+	+
Paroxysmal SVT	+	+			
Atrial fibrillation, flutter	+	+			
Hypertrophic cardiomyopathy	+				

**SIDE EFFECTS: (TABLES IVa and IVb)**

Calcium channel blocking agents do not induce biochemical abnormalities, CNS dysfunction, postural hypotension or salt and water retention. They are generally well tolerated in the **elderly**; however, constipation may be a problem with verapamil.

Ankle edema is a common side effect of most of the CCBs used for cardiovascular disorders and is due to local arteriolar dilation and redistribution of fluid, not sodium and water retention.

The most common side effects of the dihydropyridines result from their peripheral vasodilatory action and include peripheral edema, headache, flushing and dizziness. These effects occur with higher frequency with nifedipine than with the other dihydropyridines. Gingival hyperplasia has been associated with nifedipine and other CCBs.

CCBs have been associated with an increased risk of gastrointestinal bleeding in **elderly** patients in a prospective cohort study. However, this was not found in observational studies. A case-control study involving patients aged 30 to 79 years found that CCB-users had a two-fold higher relative risk of gastrointestinal bleeding compared to those receiving beta blockers. More study is needed.

Data examining cancer risk in CCB-treated patients are conflicting. Some studies suggest an increased risk, others do not.

Although some CCBs are less cardiodepressant than others (TABLES Ia and Ib), this may not necessarily be a clinical advantage in CHF patients with regard to exacerbation or progression of heart failure because of the general tendency for CCBs to activate neurohormonal systems.

**TABLE IVa: SIDE EFFECTS** (Incidence 5% or more)

	Verapamil	Diltiazem	Nifedipine	Flunarizine
Overall incidence	23-37%	20%	28%	
% patients discontinuing drug due to side effects	4-10%	1%	5%	5%
Most common: Peripheral edema		</= 9%	10-30%	
Drowsiness (including fatigue)				20%
Headache	5%	</= 8%	8%	
Weight gain				15%
Dizziness		</= 5%	7%	
Flushing			6%	
Asthenia/fatigue		3-5%		
Hypotension	5-10%			
Nausea			6%	
Constipation	7-9%			

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**TABLE IVb: SIDE EFFECTS** (Incidence 5% or more)

	Amlodipine	Felodipine	Nimodipine
Overall incidence	20-30%	52%	5-21%
% patients discontinuing drug due to side effects	1%	9%	
Most common: Peripheral edema	10%	21%	
Headache	8%	15%	
Dizziness		5%	
Hypotension			5%
Flushing		13%	
Asthenia/fatigue	5%		

**INTERACTIONS:** (Also see separate Diltiazem, Nifedipine, Nimodipine, Verapamil monographs.)

**Increased CCB bioavailability:**

Flavonoids in **grapefruit juice** are thought to inhibit cytochrome P450 CYP3A4 metabolism of CCBs in the gut, causing increased bioavailability. The interaction appears to be clinically significant in CCBs with the lowest oral bioavailability (e.g. felodipine). Clinical relevance with other CCBs is not well established because of large interindividual variation in CCB oral bioavailability and variation in the overall magnitude of the interaction. Nevertheless, patients are generally advised to avoid grapefruit juice when taking CCBs. Taking the CCB and the grapefruit juice at different times of the day is not recommended as the effect of the juice on gut enzymes may be prolonged.

**Erythromycin** and **itraconazole** may increase the bioavailability of felodipine through inhibition of cytochrome P450 enzymes in the gut and liver. The interaction has also been observed between azole antifungals and nifedipine. **Cimetidine** may increase the effects of diltiazem and nifedipine by inhibiting liver metabolism or by lowering gastric acidity. Increased oral bioavailability of verapamil has also been observed with concurrent use of cimetidine. Cimetidine and amlodipine do not appear to interact. Interactions between **ranitidine** and CCBs are not significant. **Fluoxetine** has been shown to increase adverse effects associated with nifedipine and diltiazem, perhaps through inhibition of cytochrome P450 CYP3A4 metabolism in the liver.

**Anticonvulsants:**

Diltiazem and verapamil may decrease liver metabolism of **carbamazepine** causing increased anticonvulsant levels and possible toxicity. At the same time, carbamazepine, **phenobarbital**, and **phenytoin** are well-known inducers of hepatic metabolism; concurrent use may result in faster CCB clearance. **Valproic acid** may increase nimodipine levels by inhibiting first-pass metabolism.

**Hypoglycemic agents:**

CCBs may affect insulin secretion and glucose regulation. While there are isolated case reports of worsening diabetes control with diltiazem and nifedipine, most diabetics appear to tolerate CCB therapy. More study is needed.

**Rifampin:**

Rifampin reduces serum levels of several CCBs (e.g. diltiazem, nifedipine, verapamil) through induction of metabolizing enzymes in the gut.

**Cardiovascular drugs: (TABLES Va and Vb)**

The CCBs differ somewhat in their interactions with other drugs likely to be taken by patients with cardiovascular disease. Almost all CCBs interact with beta blockers, either potentiating the hypotensive response or increasing the risk of sinus bradycardia, heart block or heart failure.

**TABLE Va: INTERACTIONS WITH CARDIOVASCULAR DRUGS**

	Verapamil	Diltiazem	Nifedipine
Amiodarone	Yes (b) Hypotension, sinus arrest	Yes (b) Hypotension, cardiac arrest	Yes (b) Hypotension, sinus arrest
Antiarrhythmics Class I (quinidine, procainamide, disopyramide, flecainide)	Yes (a, b) Heart failure, hypotension	Yes (b) Potentiation of heart failure	Yes (b) Decreased quinidine levels/effects
Antihypertensives (methyldopa, clonidine, prazosin)	Yes (b) Potentiated hypotension		Yes (b) Potentiated hypotension
Beta blockers	Yes (b) Increased AV block, bradycardia, hypotension	Yes (b) Increased AV block, bradycardia, hypotension, heart failure	Yes (b) Increased AV block, hypotension
Digoxin	Yes (b) Digoxin toxicity	Yes (b) Possible increased digoxin effect	Yes (b) Possible increased digoxin effect

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**TABLE Vb: INTERACTIONS WITH CARDIOVASCULAR DRUGS**

	Amlodipine	Felodipine
Beta blockers	Yes (b) Increased hypotension	Yes (b) Increased metoprolol levels; decreased heart rate
Digoxin	No	No

(a) = use of combination is contraindicated, avoid

(b) = use combination with caution, monitor

**PRESENTATION:** (See separate monographs on Diltiazem, Nifedipine, Nimodipine, and Verapamil).

### AMLODIPINE (Norvasc 5, 10 mg tablets)

Lowers supine systolic and diastolic blood pressures by approximately 10% in both young and elderly hypertensive patients; most (approximately 78%) patients with mild to moderate **hypertension** achieve a blood pressure reduction of greater than 10 mm Hg below baseline at a dose of 10 mg daily. Effective adjunct to enalapril or captopril therapy in patients with moderate to severe hypertension unresponsive to monotherapy. In patients whose blood pressure is not adequately controlled by hydrochlorothiazide, the addition of amlodipine 1.5 to 10 mg daily has been shown to improve blood pressure control and serum lipid profiles. At antihypertensive doses, it does not cause significant postural hypotension, sinus node depression, impaired AV conduction or impaired cardiac function. Reflex tachycardia occurs infrequently. Has been used in the management of pediatric hypertension.

The drug does not appear to increase neurohormonal activity (epinephrine, renin, aldosterone, atrial natriuretic peptide) which suggests that amlodipine may be safer than other CCBs in patients with left ventricular dysfunction or **heart failure**. A multicentre trial showed no overall influence on morbidity and mortality when amlodipine was given to patients with CHF. A three-year study examining the **antiatherosclerotic effects** of amlodipine compared to placebo (PREVENT), found no difference between the two groups on angiographic progression of coronary atherosclerosis. However, secondary findings suggest reduced carotid atherosclerosis, decreased rates of unstable angina, and reduced need for revascularization in amlodipine-treated patients with existing coronary heart disease who were also receiving beta-blockers, nitrates, and/or lipid-lowering agents.

Unlike nifedipine, amlodipine does not increase serum levels of digoxin and the drug does not appear to interact with cimetidine. In comparative hypertension trials, amlodipine was at least as well tolerated as atenolol, nadolol, verapamil, diltiazem and hydrochlorothiazide and caused a lower incidence of edema than the latter agents. Overall, there was no significant difference between amlodipine, verapamil and diltiazem in incidence of side effects and side effect-related drug discontinuation rates.

**Dose: Hypertension and angina:** Initially, 5 mg once daily, although a lower dose of 2.5 mg once daily has also been effective. If necessary, the dose can be gradually increased after 1 to 2 weeks to a maximum of 10 mg/day. In the elderly, small debilitated adults, and patients with hepatic insufficiency, a lower initial dose of 2.5 mg once daily is recommended. This lower dose should also be used when amlodipine is added to existing antihypertensive regimens. No dosage adjustment is required in patients with renal impairment. Pediatric doses range from 0.05 to 0.3 mg/kg/day (maximum 15 mg).

### FELODIPINE (Plendil, Renedil; extended release tablets 2.5, 5, 10 mg)

Felodipine produces hemodynamic effects similar to those of nifedipine, but unlike nifedipine, lacks negative inotropic effects at pharmacologically equivalent doses. In hypertensive patients, an initial slight reflex tachycardia is often seen, but heart rate returns to baseline within one week. The use of felodipine in hypertensive patients is not associated with a persistent increase in neurohormonal activity.

Extended release (ER) felodipine reduces systolic and diastolic blood pressures in patients with all degrees of primary **hypertension** and this reduction is sustained for 24 hours. The antihypertensive effect is maximal after approximately 14 days. Felodipine ER appears to be as effective as other commonly used antihypertensive agents in the treatment of mild to moderate hypertension and offers no apparent advantage over established therapy. However, in some studies, felodipine ER reduced the systolic blood pressure significantly more than captopril, the diastolic blood pressure more than enalapril, and both the systolic and diastolic blood pressures more than diuretics. Felodipine ER has also been effective as adjunctive therapy in patients whose blood pressure was inadequately controlled by metoprolol or enalapril; higher response rates and greater blood pressure reductions have been observed with combined therapy than with either drug alone. As add-on therapy, felodipine ER appears to be at least as effective as other antihypertensive drugs including nifedipine, hydrochlorothiazide, prazosin, hydralazine, propranolol, and minoxidil.

Clinical data suggest that felodipine ER may be useful either alone or in combination with beta blockers in patients with stable effort-induced angina. However, further studies are needed to define its role in angina pectoris.

Felodipine is extensively metabolized by the cytochrome P450 system; oral bioavailability is approximately 15%. Therefore, drugs that inhibit this system (e.g. cimetidine, erythromycin, itraconazole) may increase felodipine plasma levels and pharmacologic effects. Similarly, the bioavailability and half-life of felodipine are significantly reduced by coadministration with enzyme-inducing antiepileptic drugs (phenytoin, phenobarbital, and carbamazepine). Although regular release felodipine increases serum levels of concomitant digoxin, this interaction does not appear to occur with the extended release formulation. Concomitant ethanol increases the antihypertensive effect of felodipine ER. Like most other CCBs, felodipine interacts with beta blockers. Bioavailability is increased by **grapefruit juice**, which inhibits cytochrome P450 enzyme degradation in the gut. The interaction is clinically significant for felodipine; grapefruit juice should be avoided altogether.

**Dose:** Initially, 5 mg once daily, followed by subsequent dosage adjustments according to blood pressure response at intervals of at least 2 weeks. The usual maintenance dose is 2.5 to 10 mg once daily. Doses above 10 mg a day may substantially increase the incidence and severity of vasodilatory side effects (e.g. peripheral edema).

In the **elderly** and in patients with **hepatic impairment:** Initially, 2.5 mg once daily; doses above 10 mg a day should be avoided in these patients. A greater hypotensive effect may occur in elderly compared with younger patients; careful blood pressure monitoring during dosage adjustment is recommended. No dosage adjustment is necessary in patients with renal impairment.

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### FLUNARIZINE (Sibelium, Novo; 5 mg capsules)

In addition to calcium channel blocking activity, flunarizine also exhibits antihistaminic, anticonvulsant, and vestibular depressive activity. The drug selectively blocks excessive entry of calcium into tissue cells, thereby preventing cell damage due to calcium overload. The effects of flunarizine which may contribute to its efficacy in migraine prevention include: inhibition of calcium mediated vascular smooth muscle contraction, with selectivity for cerebral arteries (peripheral hemodynamics, myocardial contractility, or electrophysiology are not significantly affected); inhibition of vasoconstriction due to platelet derived mediators such as serotonin, prostaglandins, and thromboxane A<sub>2</sub>; increased regional cerebral blood flow; and possibly, prevention of hypoxia related brain cell damage, and improved blood viscosity and erythrocyte deformability.

As prophylactic therapy, flunarizine significantly reduces the frequency and duration of attacks of classic and common **migraine** in children and adults. The drug is not indicated for the treatment of acute migraine attacks. For prophylaxis against common and classic migraine, flunarizine appears to be at least as effective as pizotifen (pizotyline), cinnarizine, methysergide, nimodipine, metoprolol, and propranolol in adults, and at least as effective as aspirin or cyclandelate in children. Its efficacy is better documented than that of verapamil or nimodipine. Headache frequency decreases progressively after the start of therapy, with peak reduction occurring after 3 months. Overall, in a number of studies, migraine frequency decreased in approximately 80% of patients and migraine attacks were abolished in approximately 40%.

Flunarizine has also reduced seizure frequency when used as add-on treatment in some children and adults with partial or generalized epilepsy resistant to maximal combined therapy with conventional antiepileptic agents. The drug may be effective in treatment of vertigo related to either labyrinth damage or atherosclerotic cerebrovascular disease, being at least as effective as cinnarizine, and more effective than betahistine or pentoxifylline. Flunarizine has also been effective in the treatment of cerebrovascular insufficiency associated more with memory/concentration deficits, confusion, sleeplessness, and depression than with vertigo.

Drowsiness and weight gain (2-3 kg) are the most common side effects. Extrapyramidal side effects (including parkinsonism, orofacial tardive dyskinesia, and akathisia) have been reported in a few elderly patients following long-term therapy. The most serious side effect in clinical trials was depression which caused drug withdrawal in 1.3% of treated patients; patients with a history of depression are at increased risk.

**Dose: Migraine, cerebrovascular disturbances, vestibular disorders:** 10 mg once daily in adults and 5 mg once daily in children weighing under 40 kg. In adults experiencing significant side effects, reduction of the dosage to 5 mg at bedtime may offer some relief. In patients receiving antiepileptic drugs, such as carbamazepine and phenytoin which increase the metabolism of flunarizine (lowering its plasma levels by about 50%), a dosage of 15 to 20 mg daily is recommended in adults. In children under 40 kg who are also taking these drugs, flunarizine should be started at a dose of 5 mg daily and increased to 10 mg daily depending on therapeutic response and adverse effects. Daily doses should be administered in the evening to minimize the effects of drowsiness. An appropriate trial period is 6 to 8 weeks because the maximal effect is delayed.

### PATIENT INSTRUCTIONS:

The following patient instructions are for amlodipine (Norvasc), felodipine (Plendil, Renedil), flunarizine (Sibelium). For diltiazem, nifedipine, nimodipine, and verapamil, see individual drug monographs.

1. Amlodipine and felodipine, are used to control angina pectoris or high blood pressure (hypertension). Flunarizine is mostly used to prevent migraine headaches; the drug has also been used for other conditions such as vertigo.
2. This medication must be taken regularly and as directed even if you do not experience any chest pain (if you are being treated for angina pectoris) or are feeling well (if you are being treated for hypertension). It is by taking these medications regularly that the condition or symptoms are controlled.
3. Felodipine tablets are specially formulated for extended release and must be swallowed whole. Do not break, crush or chew them. Do not drink grapefruit juice if you are on felodipine as the effects of felodipine may be enhanced. Limit the intake of alcoholic beverages as alcohol may enhance the blood pressure lowering effect of this drug and cause dizziness or lightheadedness.
4. Do not miss any doses. However, if you do miss a dose, take it as soon as possible. If it is almost time for the next dose, skip the missed dose and resume your regular dosing schedule. Do not double doses.
5. Do not suddenly stop taking the medication and do not stop taking the medication without your physician's approval. Make sure you do not run out of medication.
6. Felodipine and amlodipine have caused tenderness, swelling, or bleeding of the gums in some patients. Brushing, flossing and having your teeth cleaned regularly may help prevent or minimize this effect.
7. Flunarizine may cause drowsiness or decreased alertness, particularly when you begin taking the medication or when you increase the dose. The daily dose is therefore best taken in the evening. Also, driving vehicles or operating machinery may be hazardous while taking this medication and caution should be taken until you see how this drug affects you.
8. The medications used to treat hypertension or angina frequently cause mild ankle swelling, dizziness, flushing, and headache but these effects usually go away after several weeks of continued use. If any of these or other effects are severe or bothersome, your physician should be contacted.
9. Other drugs, including drugs that can be purchased without a prescription (e.g. cold medications), may alter the effect of these medications or cause unwanted side effects when the two are taken together. Therefore, check with your physician or pharmacist before starting a new medication.