CALCIUM CHANNEL BLOCKING AGENTS (Systemic)

Introduction

Revised: 08/09/2000

This monograph includes information on the following:1) Bepridil b; 2) Diltiazem ; 3) Felodipine ; 4) Flunarizine a; 5) Isradipine b; 6) Nicardipine b; 7) Nifedipine ; 8) Nimodipine ; 9) Verapamil .

VA CLASSIFICATION (Primary/Secondary)
Bepridil¾CV200/ CV250
Diltiazem¾CV200/; CV300; CV409
Felodipine¾CV200/
Flunarizine¾CV200/
Isradipine¾CV200/
Nicardipine¾CV200/; CV409
Nifedipine¾CV200/; CV409
Nimodipine¾CV200
Verapamil¾CV200/; CV250; CV300 ; CV409; CV900

Commonly used brand name(s):Adalat7; Adalat CC7; Adalat PA7; Adalat XL7; Apo-Diltiaz2; Apo-Nifed7; Apo-Verap9; Calan9; Calan SR9; Cardene6; Cardizem2; Cardizem CD2; Cardizem SR2; Dilacor-XR2; DynaCirc5; Isoptin9; Isoptin SR9; Nimotop8; Novo-Diltazem2; Novo-Nifedin7; Novo-Veramil9; Nu-Diltiaz2; Nu-Nifed7; Nu-Verap9; Plendil3; Procardia7; Procardia XL7; Renedil3; Sibelium4; Syn-Diltiazem2; Vascor1; Verelan9.

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

a Not commercially available in the U.S.

b Not commercially available in Canada.

Category

Antianginal¾Bepridil; Diltiazem; Felodipine; Isradipine; Nicardipine; Nifedipine; Verapamil.

Antiarrhythmic¾Diltiazem; Verapamil.

Antihypertensive¾Diltiazem; Felodipine; Isradipine; Nicardipine; Nifedipine; Verapamil.

Hypertrophic cardiomyopathy therapy adjunct¾Verapamil.

Subarachnoid hemorrhage therapy¾Flunarizine; Nicardipine; Nimodipine.

Vascular headache prophylactic¾Flunarizine; Verapamil.

Indications

Note: Bracketed information in the Indications section refers to uses that are not included in U.S. product labeling.

Accepted

Angina pectoris, chronic (treatment)¾Bepridil 110, 204 , diltiazem 160 , [felodipine] 135 , [isradipine] 129, 130, 131, 134 , nicardipine 190 , nifedipine, and verapamil are indicated in the management of classic angina (chronic stable angina or effort-associated angina) with no evidence of vasospasm. Nicardipine [and other calcium channel blocking agents] may be used alone or in combination, with caution, with beta-adrenergic blocking agents 64, 190.

Diltiazem 160 , [felodipine] 135 , [isradipine] 129, 130, 131, 134 , [nicardipine] 70 , nifedipine, and verapamil are also indicated in the management of vasospastic angina (Prinzmetal's variant, or at-rest angina) or unstable angina in patients who are unable to tolerate or whose symptoms are not relieved by adequate doses of beta-adrenergic blocking agents or organic nitrates. They are generally indicated when vasospastic angina is confirmed by: (a) the classical pattern accompanied by elevation of ST segment; (b) ergonovine-induced angina or coronary artery spasm; or (c) coronary artery spasm demonstrated by angiography, although they may also be used when a vasospastic component is indicated but not confirmed (e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm) 196.

Tachycardia, supraventricular (treatment and prophylaxis)¾Verapamil and parenteral diltiazem are indicated in the treatment of supraventricular tachyarrhythmias. Diltiazem 161 and verapamil produce rapid conversion to sinus rhythm of paroxysmal supraventricular tachycardia (including those associated with accessory bypass tracts, such as Wolff-Parkinson-White [W-P-W] or Lown-Ganong-Levine [L-G-L] syndrome) in patients who do not respond to vagal maneuvers 161 when the atrioventricular (AV) node is required for reentry to sustain tachycardia 125.

Parenteral diltiazem 161 and verapamil also produce temporary control of rapid ventricular rate in atrial flutter or atrial fibrillation. Oral verapamil is indicated, alone or in association with digitalis, 169 for control of ventricular rate at rest and during stress in patients with chronic atrial flutter and/or atrial fibrillation (not otherwise controllable with digitalis 195), and for prophylaxis of repetitive paroxysmal supraventricular tachycardia. Diltiazem and verapamil do not produce class I, II, or III antiarrhythmic effects.

Hypertension (treatment)¾Diltiazem, felodipine 1 , isradipine 206 , nicardipine 190 , nifedipine, and verapamil are indicated, alone or in combination with other agents 159, 190, 191, 196, 206 , for treatment of hypertension .

[Cardiomyopathy, hypertrophic (treatment adjunct)]¾Verapamil is used in the treatment of hypertrophic cardiomyopathy 195 to relieve ventricular outflow obstruction. However, extreme caution is recommended when hypertrophic cardiomyopathy is complicated by left ventricular obstruction, high pulmonary wedge pressure, paroxysmal nocturnal dyspnea or orthopnea, sinoatrial (SA) nodal function impairment, or severe heart block.

Raynaud's phenomenon (treatment)¾[Felodipine] 135 , [isradipine] 129, 134 , [nicardipine] , and [nifedipine] * are used for symptomatic treatment of Raynaud's phenomenon 71.

Subarachnoid hemorrhage-associated neurologic deficits (treatment) ¾Nimodipine is indicated for improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in patients with subarachnoid hemorrhage from ruptured congenital intracranial aneurysms who are in good neurological condition post-ictus (e.g., Hunt and Hess Grades I-III) 140, 141, 142, 144, 146, 153, 154, 157.

[Flunarizine] 129, 134 and [nicardipine] 129, 134 are also used for this indication.

Headache, vascular (prophylaxis)¾Flunarizine 205 and [verapamil] 129, 132, 133, 134 are indicated for reducing frequency and severity of vascular headaches, but are not recommended for treatment of acute attacks.

Acceptance not established

A preliminary study and case report suggest diltiazem may be used in pediatric patients for the treatment of pulmonary hypertension. 230, 231, 232 However, data are insufficient to establish safety and efficacy of diltiazem for this indication. 230, 231, 232

Unaccepted

Sublingual use of nifedipine capsules for hypertensive crisis is not recommended because it has been associated with severe hypotension, acute myocardial infarction, stroke, and death 219.

* Not included in Canadian product labeling.

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Molecular weight¾Bepridil hydrochloride: 421.02

Diltiazem hydrochloride: 450.98

Felodipine: 384.26

Flunarizine hydrochloride: 477.42

Isradipine: 371.39

Nicardipine hydrochloride: 515.99

Nifedipine: 346.34

Nimodipine: 418.45

Verapamil hydrochloride: 491.07

Mechanism of action/Effect:

These agents are calcium-ion influx inhibitors (slow-channel blocking agents). Although their mechanism is not completely understood, they are thought to inhibit calcium ion entry through select voltage-sensitive areas termed "slow channels" across cell membranes. By reducing intracellular calcium concentration in cardiac and vascular smooth muscle cells, they dilate coronary arteries and peripheral arteries and arterioles, and may reduce heart rate, decrease myocardial contractility (negative inotropic effect), and slow atrioventricular (AV) nodal conduction. Serum calcium concentrations are unchanged, although there is some evidence that elevated serum calcium concentrations may alter the therapeutic effect of verapamil 169.

Calcium channel blocking agents may be classified into subgroups according to structure¾

Bepridil.

Benzothiazepine (diltiazem) 109, 115, 117, 118.

Diphenylpiperazine (flunarizine) 117, 118.

Dihydropyridine (felodipine, isradipine, nicardipine, nifedipine, nimodipine) 1, 109, 110, 111, 113, 115, 117, 118, 206.

Diphenylalkylamine (verapamil) 117.

Effects within each subgroup are generally the same¾

Bepridil is a nonselective calcium channel blocking agent that affects both cardiac and smooth muscle 113, 114, 204.

It also inhibits the fast sodium inward current in myocardial and vascular smooth muscle 204.

Piperazine derivatives act on vascular smooth muscle, with few or no direct myocardial effects 113, 114.

Dihydropyridines are selective for vascular smooth muscle compared with myocardium and therefore act primarily as vasodilators 111, 113, 114, 115.

Hypotensive effects are accompanied by reflex tachycardia 111.

Diltiazem (a benzothiazepine) and verapamil (a diphenylalkylamine) are less selective vasodilators that also have direct effects on the myocardium, including depression of sinoatrial (SA) and atrioventricular (AV) nodal conduction 111, 114, 115.

See Table 1.

Antianginal¾

Dilation of the peripheral vasculature reduces systemic pressure or cardiac afterload, which results in lessened myocardial wall tension 126 and reduced oxygen requirements of the myocardial tissues 204.

In vasospastic angina, a relaxation of coronary arteries and arterioles and inhibition of coronary artery spasm 169, 187 improves blood flow and oxygen supply to myocardial tissues 64, 72.

May also be related to enhanced left ventricular diastolic relaxation and decreased wall stiffness 29 (improved diastolic compliance 126).

Antiarrhythmic¾

The inhibited influx of calcium ions in cardiac tissues prolongs the effective refractory period and results in slowed AV nodal conduction 169.

Normal sinus rhythm is usually not affected, except in some elderly patients 101 or patients with sick sinus syndrome 204 , in whom calcium channel blockade may interfere with sinus-node impulse generation and may induce sinus or sinoatrial block 169.

Normal atrial action potential or intraventricular conduction are not altered, but in depressed atrial fibers amplitude, velocity of depolarization, and conduction velocity are decreased 169.

The antegrade effective refractory period of the accessory bypass tract may be shortened 169.

Antihypertensive¾

Reduction of total peripheral vascular resistance as a result of vasodilation.

Hypertrophic cardiomyopathy therapy adjunct¾

Improvement of left ventricular outflow. May also be related to enhanced left ventricular diastolic relaxation and decreased wall stiffness 29.

Subarachnoid hemorrhage therapy¾

Theoretically, nimodipine may prevent cerebral arterial spasm following subarachnoid hemorrhage, but that has not been confirmed by arteriography 140, 142, 144, 153.

Its exact mechanism of action in treatment of neurologic deficits caused by subarachnoid hemorrhage is not known 140, 144, 153.

Vascular headache prophylactic¾

By inhibiting the vasoconstriction that occurs in the prodromal phase, calcium channel blockade may relieve or prevent reactive vasodilation 121.

Other actions/effects:

Inhibition of platelet aggregation 66, 67, 68, 69, 146, 196.

Decrease in esophageal contraction amplitude 61, 62, 146.

Diltiazem and verapamil may inhibit cytochrome P450 3, 14, 26, 160 metabolism, thereby inhibiting the metabolism of other medications or compounds. Flunarizine has antihistaminic effects 205.

Isradipine has diuretic effects 206.

Verapamil decreases gastrointestinal transit time 171.

Absorption:

Bepridil¾Rapid and complete 110, 204 ; bioavailability 60 to 70% because of first-pass metabolism 110 ; rate, but not extent of absorption, is reduced in the presence of food 110, 204.

Diltiazem¾Well absorbed 192, 193 ; bioavailability approximately 40% because of first-pass metabolism 160 ; bioavailability may increase with chronic use and increasing dose (i.e., bioavailability is nonlinear) 159, 191.

Felodipine¾Almost completely absorbed 1 ; bioavailability approximately 20% because of first-pass metabolism 1.

Bioavailability is not affected in the presence of food; however, bioavailability more than doubled when felodipine was taken with doubly concentrated grapefruit juice as compared to when it was taken with water or orange juice (a similar, but lesser, effect is also seen with other dihydropyridines) 1.

Flunarizine¾Well absorbed 205.

Isradipine¾Absorption is 90 to 95% 206 ; bioavailability approximately 15 to 24% because of first-pass metabolism 206 ; rate, but not extent, of absorption is reduced in the presence of food 206.

Nicardipine¾Completely absorbed 190 ; bioavailability approximately 35% because of first-pass metabolism 190.

Nifedipine¾Rapidly and completely absorbed 164, 166 ; bioavailability approximately 60 to 75% because of first-pass metabolism 164, 166.

Bioavailability of extended-release formulations may be 10 to 15% lower than that of immediate-release formulations, but plasma concentrations are more stable, with smaller fluctuations over the dosing interval 220, 222, 223.

Bioavailability of both formulations is increased with hepatic function impairment 165.

Rate, but not extent, of absorption of Procardia XL may be reduced in the presence of food 196.

Nimodipine¾Rapidly absorbed 140.

Because of extensive first-pass metabolism, biovailability is only about 13% (significantly increased [up to double the peak serum concentration] in patients with hepatic function impairment) 140.

The effect of food on absorption is unknown 140.

Verapamil¾More than 90% of an oral dose is absorbed 170, 180 ; bioavailability approximately 20 to 35% because of first-pass metabolism 170, 180 ; bioavailability of oral verapamil may increase with chronic use and increasing dose (i.e., bioavailability is nonlinear) 169.

Distribution:

Bepridil¾In breast milk: Concentration is approximately one-third serum concentration 204.

Protein binding:

Bepridil¾Very high (more than 99%) 110, 204.

Diltiazem¾High (70 to 80% 158 , 35 to 40% to albumin).

Felodipine¾Very high (more than 99%) 1.

Flunarizine¾Very high (99%) 205.

Isradipine¾Very high (95%) 206.

Nicardipine¾Very high (more than 95%) 190.

Nifedipine¾Very high (92 to 98%) 165.

Nimodipine¾Very high (over 95%); independent of concentration 140, 145.

Verapamil¾Very high (approximately 90%) 175.

Biotransformation:

Hepatic 140, 145, 160, 161 ; extensive and rapid, with a prominent first-pass effect 110.

Bepridil¾At least 17 metabolites, 1 or more of which may have cardiovascular activity 120.

Diltiazem¾By cytochrome P450 mixed function oxidase 160.

A major metabolite, detected following oral and continuous intravenous administration but not rapid intravenous administration 161 , is desacetyl diltiazem, which has one quarter to one half the coronary dilatation activity of the parent compound 160.

Felodipine¾Six metabolites, accounting for 23% of an oral dose, have been identified; none has significant vasodilating activity 1.

Isradipine¾Completely metabolized; six metabolites identified 206.

Nifedipine¾No known active metabolites.

Verapamil¾Principal metabolite is norverapamil, which has approximately 20% of the hypotensive cardiovascular activity of verapamil 29, 102, 169 ; 11 other metabolites occur only in trace amounts 169.

Half-life:

Bepridil (biphasic) 204¾ Distribution¾
Approximately 2 hours 204.

Elimination¾
Terminal: Average, 42 hours (range, 26 to 64 hours) 204.

Dosing interval: Less than 24 hours 204.

Diltiazem¾
Oral (biphasic):
Extended-release capsules¾
Cardizem CD: Apparent¾5 to 8 hours 193.

Cardizem SR: Apparent¾5 to 7 hours 191.

Tablets¾
Early: 20 to 30 minutes.
Terminal: Approximately 3.5 hours 159 (5 to 8 hours with high and repetitive dosage 29).

Intravenous:
Approximately 3.4 hours 161.

Felodipine (polyphasic) 1¾
Terminal:
11 to 16 hours 1.

Flunarizine¾
19 days 205.

Isradipine (biphasic) 206¾
Early: 1.5 to 2 hours 206.

Terminal: About 8 hours 206.

Nicardipine (biphasic)¾
Early: 2 to 4 hours 190.

Terminal: 8.6 hours 190.

Nifedipine¾ Approximately 2 hours 165, 197.

Extended-release tablets¾
Adalat CC: Terminal¾Approximately 7 hours 229

Adalat PA: Terminal¾6 to 12 hours 228

Adalat XL, Procardia XL: Not available. The gastrointestinal therapeutic system (GITS) is designed to deliver nifedipine by zero-order systemic absorption over a period of approximately 18 hours 230.

Nimodipine¾
Terminal: 8 to 9 hours. Earlier, more rapid elimination rates (equivalent to a half-life of 1 to 2 hours) necessitate frequent dosing. 140

Verapamil¾
Oral:
Single dose¾Range, 2.8 to 7.4 hours.
Repetitive dosage¾Range, 4.5 to 12 hours (half-life is increased because of saturation of hepatic enzyme systems as plasma verapamil concentrations increase).

Intravenous (biphasic):
Early¾About 4 minutes.
Terminal¾2 to 5 hours.

Onset of action:

Diltiazem¾
Oral:
Extended-release capsules¾2 to 3 hours 87.

Tablets¾30 to 60 minutes.

Parenteral:
Rapid intravenous injection¾
Reduction in heart rate or conversion of paroxysmal supraventricular tachycardia to sinus rhythm: Within 3 minutes 161.

Felodipine¾
Within 2 to 5 hours 1.

Isradipine¾
2 to 3 hours 206.

Nifedipine¾
Oral:
Capsules¾20 minutes.

Verapamil¾
Oral:
1 to 2 hours.

Intravenous:
Antiarrhythmic¾Within 1 to 5 minutes and usually less than 2 minutes.
Hemodynamic¾Within 3 to 5 minutes.

Time to peak concentration:

Bepridil¾
2 to 3 hours 110, 204.

Diltiazem¾
Oral (wide individual variation in concentrations achieved 159):
Extended-release capsules¾
Cardizem CD: 10 to 14 hours 193.

Cardizem SR: 6 to 11 hours 191.

Tablets¾
2 to 3 hours 160.

Felodipine¾
2.5 to 5 hours 1.

Peak plasma concentrations at steady state are about 20% higher than after a single dose 1.

Flunarizine¾
2 to 4 hours 205.

Isradipine¾
About 1.5 hours 206.

Nicardipine¾
30 minutes to 2 hours (mean, 1 hour) 190.

Nifedipine¾
Capsules:
About 30 to 60 minutes 88.

Extended-release tablets:
Adalat CC¾2.5 to 5 hours 220

Adalat PA¾4 hours 88.

Adalat XL222 , Procardia XL¾Approximately 6 hours 196.

Nimodipine¾
Within 1 hour 140, 145.

Verapamil¾
Oral:
Extended-release capsules¾7 to 9 hours 202.

Tablets¾1 to 2 hours (wide individual variation in concentrations achieved).
Extended-release tablets¾5 to 7 hours.

Time to peak effect:

Bepridil¾
Time to steady-state plasma concentration: 8 days 204.

Diltiazem¾
Antihypertensive: Multiple doses¾Within 2 weeks 191.

Antiarrhythmic: Rapid intravenous injection¾Hypotension or reduction in heart rate: Within 2 to 7 minutes 161.

Flunarizine¾
Multiple doses: Several weeks 205.

Isradipine¾
Antihypertensive: Multiple doses¾2 to 4 weeks 206.

Nicardipine¾
Single dose: 1 to 2 hours 190.

Verapamil¾
Oral: About 30 to 90 minutes. The maximum effects from oral dosage are usually evident sometime during the first 24 to 48 hours of therapy (for some patients the time may be slightly extended because the half-life of verapamil tends to increase during this period).
Intravenous: Within 3 to 5 minutes after completion of injection.

Elimination:

Bepridil¾
Renal: 70% (none unchanged) 204.

Biliary/fecal: 22% (none unchanged) 204.

In dialysis: Not removable by hemodialysis 120.

Diltiazem¾
Biliary and renal (2 to 4% unchanged) 159, 191.

In dialysis: Does not appear to be removable by hemodialysis or peritoneal dialysis 160.

Felodipine¾
Renal: 70% (less than 0.5% unchanged) 1.

Biliary/fecal: 10% (less than 0.5% unchanged) 1.

Flunarizine¾
Drug and metabolites: Very slow and prolonged 205.

Biliary/fecal: Less than 6% in the first 48 hours 205.

Renal: Less than 0.2% in the first 48 hours 205.

Isradipine¾
Renal: 60 to 65% (none unchanged) 206.

Biliary/fecal: 25 to 30% (none unchanged) 206.

In dialysis: No information, but not likely to be removable by hemodialysis because of plasma protein binding 206.

Nicardipine¾
Renal: 60% (less than 1% unchanged) 190.

Biliary/fecal: 35% 190.

Nifedipine¾
Renal: 80% (as metabolites), only traces unchanged 196.

Biliary/fecal: 20% (as metabolites) 196.

In dialysis: Does not appear to be removed by hemodialysis or chronic ambulatory peritoneal dialysis 196 ; however, plasmapheresis may be beneficial 165.

Nimodipine¾
Renal (less than 1% unchanged) 140, 143.

Biliary/fecal 140, 142.

In dialysis: Because of extensive protein binding, unlikely to be significantly removed by hemodialysis or peritoneal dialysis 140.

Verapamil¾
Renal:
As conjugated metabolites¾70% as metabolites and 3 to 4% unchanged within 5 days 169.

Unmetabolized¾3%.

Biliary/fecal:
9 to 16%.

In dialysis:
Not removable by hemodialysis 29, 183.

Precautions to Consider

Carcinogenicity/Mutagenicity

For bepridil¾

A lifetime study in mice at doses up to 60 times the maximum recommended human dose (MRHD) (based on a 60-kg subject) found no evidence of carcinogenicity 204.

A lifetime study in rats at doses 20 times the usual recommended human dose found unilateral follicular adenomas of the thyroid 204.

Mutagenicity studies (micronucleus test for chromosomal effects, liver microsome activated bacterial assay for mutagenicity, Chinese hamster ovary cell assay for mutagenicity, sister chromatid exchange assay) were negative 204.

For diltiazem¾

A 24-month study with diltiazem in rats and a 21-month study in mice found no evidence of carcinogenicity.

There was no mutagenic response in in vitro bacterial tests. 160

For felodipine¾

A 2-year study in rats at doses of 7.7, 23.1, or 69.3 mg per kg of body weight (mg/kg) per day (up to 28 times the MRHD [based on a 50-kg subject]) found an increased incidence of benign interstitial cell tumors of the testes (Leydig cell tumors) in males, probably secondary to a reduction in testicular testosterone and corresponding increase in serum luteinizing hormone (which have not been observed in humans). In addition, a dose-related increase in the incidence of focal squamous cell hyperplasia in the esophageal groove of both males and females at all doses (humans have no anatomical structure comparable to the esophageal groove). Felodipine was not carcinogenic and did not increase the incidence of Leydig cell tumors in mice at doses up to 138.6 mg/kg per day (28 times the MRHD [based on a 50-kg subject]) for periods up to 80 and 99 weeks in males and females, respectively; no effect on the esophageal groove occurred. 1

Mutagenicity studies (Ames test, mouse lymphoma forward mutation assay, mouse micronucleus test, human lymphocyte chromosome aberration assay) were negative 1.

For flunarizine¾

A 24-month study in 4 groups of 50 male and 50 female Wistar rats at doses of 0, 5, 20, or 40 mg/kg per day (the 40-mg/kg group received 80 mg/kg for the first 2 months) did not produce an effect on tumor rate or type; however, the validity of the study is questionable because of an extremely high mortality rate (more than 90% in the males and 80% in the females) 205.

Mutagenicity studies (Ames test, sister chromatid exchange test in human lymphocytes, sex-linked recessive lethal test in Drosophila melanogaster , micronucleus test in male rats, dominant lethal test in male and female mice) were negative 205.

For isradipine¾

A 2-year study in male rats at doses of 2.5, 12.5, or 62.5 mg/kg per day (approximately 6, 31, and 156 times the MRHD, respectively, based on a 50-kg subject) found a dose-dependent increase in the incidence of benign Leydig cell tumors and testicular hyperplasia relative to untreated control animals; these findings were replicated in a subsequent study 206.

A 2-year study in mice at doses of 6, 38, and 200 times the MRHD found no evidence of oncogenicity 206.

Mutagenicity studies were negative 206.

For nicardipine¾

A 2-year study in rats with nicardipine at dosage levels of 5, 15, or 45 mg/kg per day found a dose-dependent increase in thyroid hyperplasia and neoplasia (follicular adenoma/carcinoma). One- and three-month studies in the rat suggest that the mechanism for this effect is a nicardipine-induced reduction in plasma thyroxine (T 4) concentrations with a resulting increase in thyroid-stimulating hormone (TSH) concentrations, which is known to cause hyperstimulation of the thyroid; in rats on an iodine-deficient diet, one month of nicardipine administration produced thyroid hyperplasia that was prevented by T 4 supplementation. Studies in mice for up to 18 months at doses up to 100 mg/kg per day and in dogs for 1 year at doses up 25 mg/kg per day found no evidence of neoplasia of any tissue and no evidence of thyroid changes. No effects of nicardipine on thyroid function (plasma T 4 and TSH) have been reported in humans. 190

No evidence of mutagenicity was found in a battery of genotoxicity tests conducted on microbial indicator organisms, in micronucleus tests in mice and hamsters, or in a sister chromatid exchange study in hamsters 190.

For nifedipine¾

Nifedipine was not shown to be carcinogenic when administered orally to rats for 2 years.

In vivomutagenic tests were negative. 196

For nimodipine¾

A 2-year study in rats found an increased incidence of adenocarcinoma of the uterus and Leydig-cell adenoma of the testes, but the increases were not significant. A 91-week study in mice found no evidence of carcinogenicity, although the life expectancy was shortened. 140

Mutagenicity studies, including the Ames, micronucleus, and dominant lethal tests, have been negative 140.

For verapamil¾

A 2-year study in rats with verapamil at doses up to 12 times the MRHD found no evidence of carcinogenicity 29.

There was no mutagenic response in the Ames test in 5 test strains at 3 mg per plate with or without metabolic activation.

Pregnancy/Reproduction

Fertility¾For felodipine¾

No significant effect on reproductive performance was found in male or female rats given doses of 3.8, 9.6, or 26.9 mg/kg per day 1.

For flunarizine¾

In studies in male and female Wistar rats at doses of 0 and approximately 10, 40, and 160 mg/kg given for 60 days pre-mating in the males or 14 days pre-mating and 21 days of gestation in the females, treated animals were mated with non-treated animals. In treated females at the highest dose, there were no pregnancies and a large number of deaths; at the 40-mg/kg dose, there was decreased weight gain during pregnancy, decreased rate of pregnancy, increase in the number of resorbed fetuses, decreased litter size, and decreased weight of pups at birth. In non-treated females mated with treated males, a slight increase in resorption was seen only at the highest dose. 205

For nifedipine¾

Reduced fertility occurred in rats given 30 times the maximum recommended human dose (MRHD) prior to mating.

Pregnancy¾For bepridil¾

Adequate and well-controlled studies in humans have not been done.

Studies in rats at maternal doses of 37 times the MRHD found reduced litter size at birth and decreased pup survival during lactation. No teratogenicity was observed in rats or rabbits at the same dose. 204

FDA Pregnancy Category C.

For diltiazem¾

Well-controlled studies in humans have not been done.

Studies in mice, rats, and rabbits, using doses of diltiazem 5 to 10 times greater than the recommended daily dose on a mg/kg basis, resulted in embryo and fetal deaths, reduced neonatal survival rates, and skeletal abnormalities. In addition, there was an increased incidence of stillbirths at doses of 20 or more times the recommended human dose. 160

FDA Pregnancy Category C.

For felodipine¾

Adequate and well-controlled studies in humans have not been done 1.

Studies in rabbits at doses of 0.46, 1.2, 2.3, and 4.6 mg/kg per day (from 0.4 to 4 times the MRHD [based on a 50-kg subject] on a mg per square meter of body surface area basis) found digital anomalies consisting of reduction in size and degree of ossification of the terminal phalanges in the fetuses. Frequency and severity of the changes were dose-related and occurred even at the lowest dose. These changes are similar to those occurring with other dihydropyridines and may be the result of compromised uterine blood flow. The anomalies did not occur in rats; abnormal position of the distal phalanges (but not reduction in size of the terminal phalanges) occurred in about 40% of cynomolgus monkey fetuses. 1

Studies in rats at doses of 9.6 mg/kg per day (4 times the MRHD [based on a 50-kg subject] on a mg per square meter of body surface area basis) produced a prolongation of parturition with a difficult labor and an increased frequency of fetal and early postnatal deaths 1.

Studies in rabbits at doses greater than or equal to 1.2 mg/kg per day (equal to the MRHD on a mg per square meter of body surface area basis) found significant enlargement (in excess of normal) of the

mammary glands during pregnancy, which regressed during lactation. These effects were not observed in rats or monkeys. 1

FDA Pregnancy Category C.

For flunarizine¾

Studies in humans have not been done.

There was a slight increase in resorptions and decrease in number of live fetuses in female Wistar rats given 40 mg/kg, with no effects seen at doses of 0, 10, or 20 mg/kg; there was no evidence of teratogenicity 205.

There was a dose-related increase in the number of resorptions in New Zealand rabbits given doses of 0, 2.5, or 10 mg/kg from day 6 to day 18 of pregnancy, with a corresponding decrease in number of live births; there was no evidence of teratogenicity 205.

For isradipine¾

Studies in humans have not been done.

Studies in rats at doses of 6, 20, or 60 mg/kg per day produced a significant reduction in maternal weight gain at the highest dose (150 times the MRHD), but with no lasting effects on the mother or offspring. Studies in rabbits at doses of 1, 3, or 10 mg/kg per day (2.5, 7.5, and 25 times the MRHD, respectively) found decreased maternal weight gain and increased fetal resorptions at the two highest doses. There was no evidence of embryotoxicity at doses that were not maternotoxic and no evidence of teratogenicity at any dose. With peri- and postnatal administration of doses of 20 and 60 mg/kg per day, reduced maternal weight gain during late pregnancy was associated with reduced birth weights and decreased peri- and postnatal pup survival. 206

FDA Pregnancy Category C.

For nicardipine¾

Adequate and well-controlled studies in humans have not been done.

Studies in Japanese White rabbits at doses of 150 mg/kg per day during organogenesis (but not at doses of 50 mg/kg per day [25 times the MRHD]) found nicardipine to be embryocidal and to cause marked body weight gain suppression in the treated doe. Studies in rats with nicardipine at doses 50 times the MRHD found no evidence of embryolethality or teratogenicity, but dystocia, reduced birth weights, reduced neonatal survival, and reduced neonatal weight gain occurred 190.

FDA Pregnancy Category C.

For nifedipine¾

Adequate and well-controlled studies in humans have not been done.

Nifedipine has been shown to be teratogenic in rodents and embryotoxic (increased fetal resorptions, reduced fetal weight, increase in stunted forms, increased fetal deaths, and decreased fetal survival) in rodents and rabbits at doses 30 times and 3 to 10 times the MRHD, respectively. In pregnant monkeys, small placentas and underdeveloped chorionic villi occurred at two thirds and two times the MRHD. In rats, three times or more the MRHD caused prolongation of pregnancy.

FDA Pregnancy Category C.

For nimodipine¾

Adequate and well-controlled studies in humans have not been done.

Two studies in Himalayan rabbits found an increased incidence of teratogenic malformations in the fetuses at doses of 1 and 10 (but not 3) mg/kg per day given on days 6 through 18 of pregnancy; in these same studies, stunted fetuses were found at doses of 1 and 10 (but not 3) mg/kg per day in one study, and only at 1 mg/kg per day in the other. Studies in Long Evans rats at doses of 100 mg/kg per day given on days 6 through 15 found embryotoxicity, including fetal resorption and stunted fetal growth. In other rat studies, doses of 30 mg/kg per day from days 16 to 20 or 21 produced an increased incidence of skeletal variation, stunted fetuses, and stillbirths, but no malformations. 140

FDA Pregnancy Category C.

For verapamil¾

Adequate and well-controlled studies in humans have not been done.

Verapamil crosses the placenta and can be detected in umbilical vein blood at delivery 169.

Occasionally, rapid intravenous injection of verapamil in humans may cause maternal hypotension resulting in fetal distress.

Studies in rats, using doses of verapamil up to 6 times the recommended daily dose for humans, resulted in embryo deaths and slowed growth.

FDA Pregnancy Category C.

Breast-feeding

For all calcium channel blocking agents¾

Although problems in humans have not been documented, bepridil 204 , diltiazem 28, 159, 191 , nifedipine 65, 165 , and verapamil 30, 169, 180 , and possibly other calcium channel blocking agents, are distributed into breast milk.

For felodipine only¾

It is not known whether felodipine is distributed into breast milk in humans 1.

For flunarizine only¾

It is not known whether flunarizine is distributed into breast milk in humans; however, it is distributed into the milk of dogs, at concentrations much higher than in plasma 205.

For nimodipine only¾

It is not known whether nimodipine is distributed into breast milk in humans; however, nimodipine and/or its metabolites have been found in the milk of treated rats, at concentrations much higher than maternal plasma concentrations 140.

Pediatrics

Although appropriate studies on the relationship of age to the effects of calcium channel blocking agents have not been performed in the pediatric population, pediatrics-specific problems that would limit the usefulness of calcium channel blocking agents in children are not expected. However, in rare instances, severe adverse hemodynamic effects have occurred after intravenous administration of verapamil in neonates and infants 30.

Geriatrics

For diltiazem 60 , nimodipine 146, 147, 149 , verapamil 59, 169, 180 , and possibly other calcium channel blocking agents¾

Half-life of calcium channel blocking agents may be increased in the elderly as a result of decreased clearance.

For felodipine only¾

Plasma concentrations increase with age 1.

Mean clearance at mean age of 76 was found to be only 45% of that at mean age of 26 1.

For isradipine only¾

Bioavailability may be increased in patients over 65 years of age 206.

For nicardipine only¾

Studies in patients 65 years of age and older found no difference in half-life or protein binding from that in young normal volunteers 190.

For nimodipine only¾

Risk of hypotension may be increased 146, 147, 149.

For all calcium channel blocking agents¾

Elderly patients are more likely to have age-related renal function impairment, which may require caution in patients receiving calcium channel blocking agents 86.

Dental

Gingival enlargement is a rare side effect that has been reported with diltiazem, felodipine, nifedipine, and verapamil. It usually starts as gingivitis or gum inflammation in the first 1 to 9 months of treatment. A strictly enforced program of teeth cleaning by a professional combined with plaque control by the patient will minimize growth rate and severity of gingival enlargement. Periodontal surgery may be indicated in some cases, and should be followed by careful plaque control to inhibit recurrence of gum enlargement. 1, 5, 6, 7, 8, 9, 10, 11, 30, 95, 205

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Information concerning interactions between calcium channel blocking agents and other medications is still limited. Therefore, some of the following potential interactions are stated for cautionary reference until additional information is available.

Combinations containing any of the following medications, depending on the amount present, may also interact with these medications.

Anesthetics, hydrocarbon inhalation

(concurrent use with calcium channel blocking agents may produce additive hypotension; although calcium channel blocking agents may be useful to prevent supraventricular tachycardias, hypertension, or coronary spasm during surgery, caution is recommended during use 35, 36, 37, 38, 39, 160, 180, 206)

Anti-inflammatory drugs, nonsteroidal (NSAIDs), especially indomethacin

(indomethacin, and possibly other NSAIDs, may antagonize the antihypertensive effect of calcium channel blocking agents by inhibiting renal prostaglandin synthesis and/or by causing sodium and fluid retention; the patient should be carefully monitored to confirm that the desired effect is being obtained 122)

>> Beta-adrenergic blocking agents, systemic or ophthalmic

(concurrent use of oral dosage forms with oral bepridil 204 , diltiazem 160 , or verapamil 180 or intravenous verapamil usually results in no serious negative inotropic, chronotropic, or dromotropic effects. However, caution and careful monitoring are necessary since the additive effect may prolong sinoatrial [SA] and atrioventricular [AV] conduction [which may lead to severe hypotension, bradycardia, and cardiac failure], especially in patients with impaired ventricular function or abnormal cardiac conduction or sinus node depression 29.

When verapamil and beta-adrenergic blocking agents are to be given intravenously, they should be administered at least a few hours apart since they may have additive depressant effects on myocardial contractility or SA or AV conduction, and asystole has been reported with concurrent use)

(in a single small study, diltiazem was reported to significantly increase the bioavailability of propranolol 159 ; in other studies, verapamil was found to decrease clearance of both metoprolol and propranolol, with a variable effect on atenolol 171)

(concurrent use with dihydropyridines, although usually well tolerated, may produce excessive hypotension, and in rare cases may increase the possibility of congestive heart failure 1.

Occasionally, angina has occurred upon initiation of nicardipine 190 or nifedipine therapy, especially after recent abrupt discontinuation of beta-adrenergic blocking agent therapy. If possible, it is recommended that beta-adrenergic blocking agent dosage be discontinued gradually, but especially before nicardipine or nifedipine therapy is begun. However, if concurrent use is necessary, nicardipine or nifedipine may be preferred over other calcium channel blocking agents in some patients because both have less effect on heart rate and conduction)

(if significant systemic absorption of an ophthalmic beta-adrenergic blocking agent 174, 180 occurs, concurrent use of calcium channel blocking agents may result in atrioventricular conduction disturbances, left ventricular failure, and hypotension; in some patients, if a calcium antagonist is necessary, nicardipine or nifedipine may be preferred because both have less effect on heart rate and conduction, although they may also cause greater hypotension; concurrent use of calcium channel blocking agents and ophthalmic beta-adrenergic blocking agents should be avoided in patients with impaired cardiac function)

Calcium supplements

(concurrent use in quantities sufficient to elevate serum calcium concentrations above normal 30 may reduce the response to verapamil and probably other calcium channel blocking agents 12, 17, 31)

>> Carbamazepine 23, 24, 25, 26, 54, 55, 169, 180 or

>> Cyclosporine 13, 20, 21, 22, 41, 42, 169, 180, 190 or

>> Quinidine 13, 27 or

Theophylline 13, 171 or

Valproate 13

(diltiazem or verapamil may inhibit cytochrome P450 3, 14, 26, 160 metabolism, resulting in increased concentrations and toxicity of these medications)

(an idiosyncratic reaction has been reported in which concurrent use of nifedipine and quinidine resulted in significantly reduced serum quinidine concentrations; caution is recommended when nifedipine therapy is initiated or discontinued in a patient stabilized on quinidine 49, 50, 51, 52, 165)

Cimetidine

(concurrent use may result in accumulation of the calcium channel blocking agent as a result of inhibition of first-pass metabolism; caution and careful titration of the calcium channel blocking agent dose is recommended on initiation of therapy in patients receiving cimetidine 1, 146, 151, 190, 191 ; ranitidine and famotidine do not appear to significantly affect calcium channel blocking agent metabolism 73)

>> Digitalis glycosides

(concurrent use of digoxin with some calcium channel blocking agents [especially verapamil and, to a lesser extent, bepridil 120 , diltiazem, and nifedipine 165] has been reported to increase the serum concentration of digoxin 159, 180 ; the effect of verapamil on digoxin kinetics is enhanced in patients with hepatic function impairment 169, 180 ; felodipine significantly increased peak plasma concentrations of digoxin, although there was no significant change in the area under the plasma concentration-time curve [AUC] 1 ; isradipine 206 and nicardipine 190 do not appear to have a significant effect. Digoxin serum concentrations should be monitored and dosage may need to be altered when concurrent dosage of the calcium channel blocking agent is initiated, changed, or discontinued. Concurrent use of oral digitalis preparations with oral diltiazem or verapamil or intravenous verapamil has resulted in no serious adverse effects when patients were closely monitored; however, both groups of medications slow AV conduction. Patients receiving them concurrently should be monitored for AV block or excessive bradycardia, especially during the first week of concurrent dosage. To avoid toxicity, dosage reduction of digitalis glycoside may be necessary)

>> Disopyramide or

Flecainide 177, 180

(disopyramide should not be administered within 48 hours before or 24 hours following verapamil administration since both medications possess negative inotropic properties; deaths have been reported; caution is also recommended when disopyramide is used concurrently with diltiazem, nicardipine 190 , or nifedipine 30 ; caution is also recommended when flecainide 171, 177, 180 is used concurrently with a calcium channel blocking agent)

Estrogens

(estrogen-induced fluid retention tends to increase blood pressure; the patient should be carefully monitored to confirm that the desired effect is being obtained 122)

>> Grapefruit juice

(concurrent administration with 200 mL of grapefruit juice has been shown to increase felodipine plasma concentration more than twofold by inhibiting first-pass metabolism in the gastrointestinal wall and/or the liver; a lesser effect also has been seen with two other dihydropyridines, nifedipine and nisoldipine 226)

Highly protein-bound medications, such as:

Anticoagulants, coumarin- and indandione-derivative

Anticonvulsants, hydantoin

Anti-inflammatory drugs, nonsteroidal

Quinine

Salicylates

Sulfinpyrazone

(caution is advised when these medications are used concurrently with nifedipine or verapamil since changes in serum concentrations of the free, unbound medications may occur)

>> Hypokalemia-producing medications, such as:

Amphotericin B, parenteral

Carbonic anhydrase inhibitors

Corticosteroids, glucocorticoid, especially those with significant mineralocorticoid activity

Corticosteroids, mineralocorticoid

Corticotropin (ACTH)

Diuretics, potassium-depleting (such as bumetanide, ethacrynic acid, furosemide, indapamide, mannitol, or thiazides)

Sodium phosphates

(risk of bepridil-induced arrhythmias may be increased 204)

Hypotension-producing medications, other (see Appendix II)

(antihypertensive effects may be potentiated when these medications are used concurrently with hypotension-producing calcium channel blocking agents; although some antihypertensive and/or diuretic combinations are frequently used for therapeutic advantage, when any hypotension-producing medication is used concurrently dosage adjustments may be necessary)

Lithium

(concurrent use with calcium channel blocking agents 180 may result in neurotoxicity in the form of nausea, vomiting, diarrhea, ataxia, tremors, and/or tinnitus; caution is recommended 82, 83, 84, 85, 92)

Neuromuscular blocking agents

(verapamil may potentiate the activity of curare-like and depolarizing neuromuscular blocking agents; dosage reduction of either or both medications may be necessary during concurrent use 180)

Phenobarbital

(may increase clearance of verapamil 180)

Prazosin, and possibly other alpha-adrenergic blocking agents

(concurrent use with calcium channel blocking agents may produce an increased hypotensive effect, possibly related to impairment of compensatory responses by alpha-blockade 18, 34, 169, 180 and/or inhibition of prazosin metabolism by calcium channel blocking agents 13, 18, 19 ; caution is recommended)

>> Procainamide 204 or

>> Quinidine 204 or

>> Other medications causing Q-T interval prolongation 204

(risk of increased Q-T interval prolongation 204)

(caution is recommended when procainamide 74 or quinidine 74, 110 is used with a calcium channel blocking agent since both groups of medications possess negative inotropic properties)

>> Rifampin, and possibly other hepatic enzyme inducers

(rifampin may reduce the bioavailability of oral verapamil by induction of first-pass metabolism 180 ; other calcium channel blocking agents may also be affected, depending on the extent of first-pass metabolism 56, 57, 58, 169)

Sympathomimetics

(concurrent use may reduce antihypertensive effects of calcium channel blocking agents; the patient should be carefully monitored to confirm that the desired effect is being obtained 122)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

With physiology/laboratory test values

Antinuclear antibody (ANA) titers and

Direct Coombs test, with or without hemolytic anemia

(positive results have been reported during nifedipine therapy 163)

Arterial blood pressure

(may be reduced by calcium channel blocking agents [except bepridil and flunarizine] 140, 153)

Electrocardiograph (ECG) effects

P-R interval

(may be increased by diltiazem and verapamil)

Note: Increase tends to be proportional to serum concentration.

Q-T interval

(may be increased by bepridil 110, 204)

T-wave morphology

(may be altered by bepridil 110, 204)

Hepatic enzymes

(may rarely be increased after several days of therapy; concentrations return to normal upon withdrawal of therapy)

Prolactin

(serum concentrations may be slightly increased by flunarizine 205)

Note: Total serum calcium concentrations are not affected by the calcium channel blocking agents.

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).

See Table 2.

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):

>> Blood pressure determinations and

>> ECG readings and

>> Heart rate determinations 123

(recommended primarily during dosage titration or when dosage is increased from established maintenance dosage level, or during addition of medications affecting cardiac conduction or blood pressure; also recommended during intravenous verapamil administration)

(blood pressure determinations are recommended at periodic intervals in patients being treated for hypertension; selected patients may be trained to perform blood pressure measurements at home and report the results at regular physician visits)

Hepatic function determinations or

Renal function determinations

(may be required at periodic intervals during long-term therapy)

For bepridil

Potassium concentrations, serum

(recommended at periodic intervals during therapy to watch for hypokalemia 204)

For nimodipine

Neurological examinations

(recommended at periodic intervals during treatment 142, 144, 153)

Side/Adverse Effects

See Table 3.

Patient Consultation

As an aid to patient consultation, refer to USP DI, Advice for the Patient, Calcium Channel Blocking Agents (Systemic).

In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):

Before using this medication

>> Conditions affecting use, especially:

Sensitivity to the calcium channel blocking agent prescribed

Pregnancy¾High doses in animals cause birth defects, prolonged pregnancy, poor bone development, and stillbirth

Use in the elderly¾Elderly patients may be more sensitive to effects

Other medications, especially parenteral amphotericin B (for bepridil), beta-adrenergic blocking agents, carbamazepine, carbonic anhydrase inhibitors, corticosteroids (for bepridil), cyclosporine, digitalis glycosides, disopyramide, grapefruit juice potassium-depleting diuretics (for bepridil), procainamide, or quinidine

Other medical problems, especially arrhythmias (for bepridil), other cardiovascular problems, or hypokalemia (for bepridil)

Proper use of this medication

>> Compliance with therapy; importance of not taking more medication than amount prescribed

>> Proper dosing

Missed dose: Taking as soon as possible; not taking if almost time for next scheduled dose; not doubling doses

>> Proper storage

For bepridil

If nausea occurs, may be taken with meals or at bedtime 204

For extended-release diltiazem capsules

Swallowing capsules whole without crushing or chewing

>> Caution if switching brands; one is for once-daily dosing and one is for twice-daily dosing

For extended-release verapamil capsules

Swallowing capsules whole without crushing or chewing

For extended-release felodipine or nifedipine tablets

Swallowing tablets whole, without breaking, crushing, or chewing

For Adalat XL and Procardia XL¾Patient may notice empty shell in stool left over after medication is absorbed 196

Taking Adalat CC on an empty stomach

For extended-release verapamil tablets

Swallowing tablets whole, without crushing or chewing; 240-mg tablet may be broken in half on instructions from physician

Taking with food or milk

For felodipine

Importance of not taking felodipine with grapefruit juice

For use as an antihypertensive

Importance of diet; possible need for sodium restriction and/or weight reduction

>> Patient may not experience symptoms of hypertension; importance of taking medication even if feeling well

>> Does not cure, but helps control hypertension; possible need for lifelong therapy; serious consequences of untreated hypertension

Precautions while using this medication

Regular visits to physician to check progress during therapy

Checking with physician before discontinuing medication; gradual dosage reduction may be necessary

>> Discussing exercise or physical exertion limits with physician; reduced occurrence of chest pain may tempt patient to be overactive

Possible headache; checking with physician if continuing or severe

>> Maintaining good dental hygiene and seeing dentist frequently for teeth cleaning to prevent tenderness, bleeding, and gum enlargement

For use as an antihypertensive

>> Not taking other medications, especially nonprescription sympathomimetics, unless discussed with physician

For patients taking bepridil, diltiazem, or verapamil

>> Checking pulse as directed; checking with physician if less than 50 beats per minute

For patients taking flunarizine

Caution when driving or doing other things requiring alertness because of risk of drowsiness 205

Side/adverse effects

Signs of potential side effects, especially angina, arrhythmias, congestive heart failure or pulmonary edema, extrapyramidal effects (for flunarizine), galactorrhea (for flunarizine), peripheral edema, tachycardia, bradycardia, excessive hypotension, gingival enlargement, allergic reaction, mental depression (for flunarizine), arthritis (for nifedipine), thrombocytopenia, and transient blindness (for nifedipine)

General Dosing Information

The results of several meta-analyses of clinical trials in post-myocardial infarction patients and patients with angina and of observational studies in hypertensive patients have suggested that taking short-acting nifedipine may increase the risk of adverse cardiovascular events and/or mortality, especially when given in high doses 203.

Consequently, the National Heart, Lung, and Blood Institute (NHLBI) recommends that short-acting nifedipine be used with extreme caution in the treatment of hypertension or angina, especially when given in higher doses 203.

Other drugs, such as beta-adrenergic blocking agents and diuretics, have been found to reduce the risk of major cardiovascular events and mortality in the treatment of hypertension and are recommended as preferred treatment by The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure203.

For oral dosage forms only

Oral dosage must be titrated for each patient as needed and tolerated.

Concurrent administration of nitroglycerin sublingually or long-acting nitrates with calcium channel blocking agents may produce an additive antianginal effect. Nitroglycerin may be used sublingually as required to abort acute angina attacks during calcium channel blocking agent therapy. Nitrate medication may be used during calcium channel blocking agent therapy for angina prophylaxis.

Although no "rebound effect" has been reported upon discontinuation of calcium channel blocking agents, a gradual decrease of dosage with physician supervision is recommended 75.

Diet/Nutrition

Concurrent administration of felodipine with 200 mL of grapefruit juice has been shown to increase felodipine plasma concentration more than twofold by inhibiting first-pass metabolism in the gastrointestinal wall and/or the liver; a lesser effect also has been seen with two other dihydropyridines, nifedipine and nisoldipine 226

For treatment of overdose or acute adverse effects

The following treatments have been proven effective for the indicated adverse effect:

· Hypotension, symptomatic¾Intravenous fluids. Intravenous dopamine or dobutamine, calcium chloride, isoproterenol, metaraminol, or norepinephrine. For parenteral verapamil, placement of patient in Trendelenburg position.

· Tachycardia, rapid ventricular rate in patients with antegrade conduction in atrial flutter fibrillation, and accessory pathway with Wolff-Parkinson-White or Lown-Ganong-Levine syndrome¾Direct-current cardioversion or intravenous procainamide. Intravenous fluids given by slow-drip.

· Bradycardia, rarely second- or third-degree atrioventricular (AV) block, with a few patients progressing to asystole¾Intravenous atropine, isoproterenol, norepinephrine, or calcium chloride or use of electronic cardiac pacemaker.

BEPRIDIL

Summary of Differences

Pharmacology/pharmacokinetics¾

Nonselective calcium channel blocking agent; also affects fast sodium inward current.

Depresses sinoatrial (SA) and atrioventricular (AV) nodes; negative inotropic effect; causes bradycardia.

Precautions¾

Laboratory value alterations¾Increases Q-T interval and alters T-wave morphology.

Medical considerations/contraindications¾Contraindicated in patients with history of serious ventricular arrhythmias or Q-T interval prolongation. Also, contraindicated in patients with second- or third-degree atrioventricular (AV) block or sinoatrial (SA) nodal function impairment, except in patients with a functioning artificial ventricular pacemaker. Extreme caution necessary in patients with hypokalemia.

Side/adverse effects¾

Differences in frequencies are due to differences in pharmacological effects. Also causes agranulocytosis (rare); arrhythmias, including torsades de pointes (less common).

Oral Dosage Forms

BEPRIDIL HYDROCHLORIDE TABLETS

Usual adult dose

Antianginal¾Oral, initially 200 mg once a day, the dosage being increased after ten days, if necessary, to 300 mg once a day 204.

Usual adult prescribing limits

400 mg daily 204.

Usual pediatric dose

Safety and efficacy have not been established 204.

Usual geriatric dose

See Usual adult dose 204.

Strength(s) usually available

U.S.¾200 mg (Rx)[Vascor]

300 mg (Rx)[Vascor]

400 mg (Rx)[Vascor]

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a well-closed container, unless otherwise specified by manufacturer. Protect from light 204.

DILTIAZEM

Summary of Differences

Pharmacology/pharmacokinetics¾

Benzothiazepine structure.

Depresses sinoatrial (SA) and atrioventricular (AV) nodes; little or no negative inotropic effect; usually does not significantly alter heart rate, but may cause slight bradycardia.

Precautions¾

Laboratory value alterations¾Increases P-R interval.

Medical considerations/contraindications¾Contraindicated in patients with second- or third-degree atrioventricular (AV) block, sinoatrial (SA) nodal function impairment, or Wolff-Parkinson-White or Lown-Ganong-Levine syndrome accompanied by atrial flutter or fibrillation, except in patients with a functioning artificial ventricular pacemaker.

Side/adverse effects¾

Differences in frequencies are due to differences in pharmacological effects.

Additional Dosing Information

See also General Dosing Information.

Dermatologic side effects usually disappear even with continued use. However, if skin eruptions persist, it is recommended that diltiazem therapy be withdrawn, since progression to erythema multiforme and/or exfoliative dermatitis or Stevens-Johnson syndrome have been reported rarely 107, 159.

Oral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling.

DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE CAPSULES

Usual adult and adolescent 77 dose

Antihypertensive¾Cardizem CD or Dilacor-XR : Oral, 180 to 240 mg once a day, the dosage being adjusted after fourteen days as needed and tolerated 139, 193.

Note: The total daily dose usually ranges from 240 to 360 mg 193.

Cardizem SR: Oral, initially 60 to 120 mg two times a day, the dosage being adjusted after fourteen days as needed and tolerated 191.

Note: Geriatric patients may be more sensitive to the effects of the usual adult dose.

Usual adult prescribing limits

360 mg daily.

Usual pediatric dose

Dosage has not been established 191.

Strength(s) usually available

U.S.¾60 mg (Rx)[Cardizem SR (sucrose)] [Generic]

90 mg (Rx)[Cardizem SR (sucrose)] [Generic]

120 mg (Rx)[Cardizem CD] [Cardizem SR (sucrose)] [Dilacor-XR] [Generic]

180 mg (Rx)[Cardizem CD (sucrose)] [Dilacor-XR]

240 mg (Rx)[Cardizem CD (sucrose)] [Dilacor-XR]

300 mg (Rx)[Cardizem CD (sucrose)]

Canada¾90 mg (Rx)[Cardizem SR]

120 mg (Rx)[Cardizem SR]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a well-closed container, unless otherwise specified by manufacturer.

Auxiliary labeling:

· Do not take other medicines without physician's advice.

Note: Check refill frequency to determine compliance in hypertensive patients.

Cardizem CD and Cardizem SR can be used interchangeably on a total daily mg-per-mg dosing basis 124.

DILTIAZEM HYDROCHLORIDE TABLETS USP

Usual adult and adolescent 77 dose

Antianginal or
[Antihypertensive] *¾Oral, initially 30 mg three or four times a day, the dosage being increased gradually at one- or two-day intervals as needed and tolerated 160.

Note: Geriatric patients may be more sensitive to the effects of the usual adult dose.

Usual adult prescribing limits

360 mg daily.

Usual pediatric dose

Dosage has not been established.

Strength(s) usually available

U.S.¾30 mg (Rx)[Cardizem] [Generic]

60 mg (Rx)[Cardizem (scored)] [Generic]

90 mg (Rx)[Cardizem (scored)] [Generic]

120 mg (Rx)[Cardizem (scored)] [Generic]

Canada¾30 mg (Rx)[Apo-Diltiaz] [Cardizem] [Novo-Diltazem] [Nu-Diltiaz] [Syn-Diltiazem] [Generic]

60 mg (Rx)[Apo-Diltiaz] [Cardizem (scored)] [Novo-Diltazem (scored)] [Nu-Diltiaz] [Syn-Diltiazem (scored)] [Generic]

90 mg (Rx)[Cardizem]

120 mg (Rx)[Cardizem]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container. Protect from light.

Auxiliary labeling:

· Do not take other medicines without physician's advice.

Note: Check refill frequency to determine compliance in hypertensive patients.

Parenteral Dosage Forms

DILTIAZEM HYDROCHLORIDE INJECTION

Usual adult and adolescent 77 dose

Antiarrhythmic¾Intravenous (rapid), 250 mcg (0.25 mg) per kg of actual body weight administered slowly over a two-minute period with continuous ECG and blood pressure monitoring 161.

If response is not adequate, 350 mcg (0.35 mg) per kg of actual body weight may be administered fifteen minutes after completion of initial dose 161.

Subsequent doses should be individualized 161.

Note: Some patients may respond to an initial dose of 150 mcg (0.15 mg) per kg of actual body weight, although the duration of action may be shorter 161.

Intravenous infusion, continuous (for continued reduction of heart rate [up to twenty-four hours] in patients with atrial fibrillation or atrial flutter), initially 10 mg per hour beginning immediately after the last rapid intravenous dose 161.

The rate of infusion may be increased in increments of 5 mg per hour as needed, up to a maximum rate of 15 mg per hour 161.

Note: Some patients may respond to an initial rate of 5 mg per hour 161.

Usual pediatric dose

Safety and efficacy have not been established 161.

Strength(s) usually available

U.S.¾5 mg per mL (Rx)[Cardizem] [Generic]

Canada¾5 mg per mL (Rx)[Cardizem] [Generic]

Packaging and storage:

Store between 2 and 8 °C (36 and 46 °F) 161 , unless otherwise specified by manufacturer. May be stored at room temperature for 1 month; destroy after 1 month at room temperature 161.

Protect from freezing 161.

Preparation of dosage form:

Diltiazem hydrochloride injection may be prepared for administration by continuous intravenous infusion by diluting the appropriate quantity in the desired volume of 0.9% sodium chloride injection, 5% dextrose injection, or 5% dextrose in 0.45% sodium chloride injection, and mixing thoroughly, as follows:

Diluent volume	Quantity of cardizem injection	Final concentrations	Administration	
			Dose a	Infusion rate
100 mL	125 mg (25 mL)	1.0 mg/mL	10 mg/hr	10 mL/hr
			15 mg/hr	15 mL/hr

250 mL	250 mg (50 mL)	0.83 mg/mL	10 mg/hr 15 mg/hr	12 mL/hr 18 mL/hr
500 mL	250 mg (50 mL)	0.45 mg/mL	10 mg/hr 15 mg/hr	22 mL/hr 33 mL/hr

a 5 mg/hr may be appropriate for some patients.

Stability:

After dilution for administration by intravenous infusion, diltiazem hydrochloride injection should be refrigerated until use and should be used within 24 hours 161.

Incompatibilities:

Diltiazem hydrochloride injection is physically incompatible with furosemide solution 161.

FELODIPINE

Summary of Differences

Pharmacology/pharmacokinetics¾
Dihydropyridine structure.
Potent peripheral vasodilator; does not depress sinoatrial (SA) or atrioventricular (AV) node; reflex increase in heart rate in response to vasodilation masks negative inotropic effect.

Precautions¾
Medical considerations/contraindications¾No caution necessary in renal function impairment.

Side/adverse effects¾
Differences in frequencies are due to differences in pharmacological effects.

Oral Dosage Forms

FELODIPINE EXTENDED-RELEASE TABLETS

Usual adult dose

Antihypertensive¾Initial: Oral, 5 mg once a day, the dosage being adjusted as needed, usually at intervals of not less than two weeks 1.

Maintenance: Oral, 5 to 10 mg once a day 1.

Antianginal¾Oral, 10 mg once a day 136.

Note: Geriatric patients may be more sensitive to the effects of the usual adult dose.

Usual adult prescribing limits

20 mg once a day 1.

Usual pediatric dose

Safety and efficacy have not been established 1.

Strength(s) usually available

U.S.¾2.5 mg[Plendil]

5 mg (Rx)[Plendil]

10 mg (Rx)[Plendil]

Canada¾2.5 mg[Plendil] [Renedil]

5 mg (Rx)[Plendil] [Renedil]

10 mg (Rx)[Plendil] [Renedil]

Packaging and storage:

Store below 30 °C (86 °F) 1 , unless otherwise specified by manufacturer. Store in a tight container 1.

Protect from light 1.

Auxiliary labeling:

· Do not take other medicines without physician's advice.

Note: Check refill frequency to determine compliance in hypertensive patients.

FLUNARIZINE

Summary of Differences

Indications¾
Indicated for prophylaxis of migraine.

Pharmacology/pharmacokinetics¾
Diphenylpiperazine structure.
Does not depress sinoatrial (SA) or atrioventricular (AV) node; no negative inotropic effect; no reflex increase in heart rate; no antihypertensive effect.
Cerebroselective.

Precautions¾

Medical considerations/contraindications¾Caution required in patients with history of mental depression or with Parkinsonian syndrome or other extrapyramidal disorders.

Side/adverse effects¾

Differences in frequencies are due to differences in pharmacological effects. Also causes parkinsonian extrapyramidal effects (less common), galactorrhea (rare), mental depression (less common), drowsiness (more common), dryness of mouth (less common), increased appetite and/or weight gain (more common).

Oral Dosage Forms

FLUNARIZINE HYDROCHLORIDE CAPSULES

Usual adult dose

Vascular headache prophylactic¾Oral, 10 mg once a day in the evening 205.

Note: Geriatric patients may be more sensitive to the effects of the usual adult dose.

Usual pediatric dose

Dosage has not been established 205.

Strength(s) usually available

U.S.¾Not commercially available.

Canada¾5 mg (Rx)[Sibelium]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a well-closed container, unless otherwise specified by manufacturer. Protect from light 205.

ISRADIPINE

Summary of Differences

Pharmacology/pharmacokinetics¾

Dihydropyridine structure.

Potent peripheral vasodilator; does not depress sinoatrial (SA) or atrioventricular (AV) node; reflex increase in heart rate in response to vasodilation masks negative inotropic effect.

Side/adverse effects¾

Differences in frequencies are due to differences in pharmacological effects.

Oral Dosage Forms

ISRADIPINE CAPSULES

Usual adult dose

Antihypertensive¾Oral, initially 2.5 mg two times a day, alone or in combination with a thiazide diuretic, the dosage being increased, if necessary, in increments of 5 mg per day at two- to four-week intervals 206.

Note: Geriatric patients may be more sensitive to the effects of the usual adult dose.

Usual adult prescribing limits

10 mg two times a day 206.

Usual pediatric dose

Safety and efficacy have not been established 206.

Strength(s) usually available

U.S.¾2.5 mg (Rx)[DynaCirc]

5 mg (Rx)[DynaCirc]

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F) between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container 206.

Protect from light 206.

Auxiliary labeling:

· Do not take other medicines without physician's advice.

Note: Check refill frequency to determine compliance in hypertensive patients.

NICARDIPINE

Summary of Differences

Pharmacology/pharmacokinetics¾

Dihydropyridine structure.

Potent peripheral vasodilator; does not depress sinoatrial (SA) or atrioventricular (AV) node; reflex increase in heart rate in response to vasodilation masks negative inotropic effect.

Precautions¾

Geriatrics¾No change in half-life or protein binding.

Medical considerations/contraindications¾Caution necessary in patients with acute cerebral infarction or hemorrhage.

Side/adverse effects¾

Differences in frequencies are due to differences in pharmacological effects.

Oral Dosage Forms

NICARDIPINE HYDROCHLORIDE CAPSULES

Usual adult and adolescent 78 dose

Antianginal or
Antihypertensive¾Oral, initially 20 mg three times a day, the dosage being adjusted as needed and tolerated 190.

Usual pediatric dose

Dosage has not been established 190.

Strength(s) usually available

U.S.¾20 mg (Rx)[Cardene] [Generic]

30 mg (Rx)[Cardene] [Generic]

Canada¾Not commercially available

Packaging and storage:

Store between 15 and 25 °C (59 and 77 °F), in a well-closed, light-resistant container, unless otherwise specified by manufacturer.

Auxiliary labeling:

· Do not take other medicines without physician's advice.

Note: Check refill frequency to determine compliance in hypertensive patients.

NIFEDIPINE

Summary of Differences

Pharmacology/pharmacokinetics¾
Dihydropyridine structure.
Potent peripheral vasodilator; does not depress sinoatrial (SA) or atrioventricular (AV) node; reflex increase in heart rate in response to vasodilation masks negative inotropic effect.

Precautions¾
The results of several meta-analyses of clinical trials in post-myocardial infarction patients and patients with angina and of observational studies in hypertensive patients have suggested that taking short-acting nifedipine may increase the risk of adverse cardiovascular events and/or mortality, especially when given in high doses 203.

Consequently, the National Heart, Lung, and Blood Institute (NHLBI) recommends that short-acting nifedipine be used with extreme caution in the treatment of hypertension or angina, especially at higher doses 203.

Other drugs, such as beta-adrenergic blocking agents and diuretics, have been found to reduce the risk of major cardiovascular events and mortality in the treatment of hypertension and are recommended as preferred treatment by The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure203.

Side/adverse effects¾
Differences in frequencies are due to differences in pharmacological effects. Also causes arthritis associated with elevated antinuclear antibody (ANA) titers (rare), transient blindness at peak plasma concentrations (rare).

Additional Dosing Information

See also General Dosing Information.

In solution, degradation of nifedipine occurs more rapidly at 25 °C (77 °F) than at 4 °C (39 °F). However, when nifedipine solutions are protected from light and refrigerated, concentrations of nifedipine decline to approximately 90% of the original concentrations within 6 hours of preparation. It is recommended that extemporaneous preparations be made immediately before use. 98

Oral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling.

NIFEDIPINE CAPSULES USP

Usual adult and adolescent 79 dose

Antianginal or
[Antihypertensive] *¾Essential hypertension: Oral, initially 10 mg three times a day, the dosage being increased over a seven- to fourteen-day period as needed and tolerated.

Note: For hospitalized patients under close supervision, dosage may be increased by 10-mg increments over four- to six-hour periods until symptoms are controlled.

When justified by symptom frequency and/or severity, dosage titration may be accomplished over a three-day period (medication given three times a day and increased stepwise from 10 mg to 20 mg, then to 30 mg per dose as needed and tolerated), but only if the patient is monitored frequently.

Geriatric patients may be more sensitive to the effects of the usual adult dose.

Usual adult prescribing limits

Single dose, up to 30 mg; total daily dose, up to 180 mg (a total daily dose greater than 120 mg is rarely required).

Usual pediatric dose

Dosage has not been established.

Strength(s) usually available

U.S.¾10 mg (Rx)[Adalat] [Procardia] [Generic]

20 mg (Rx)[Adalat] [Procardia] [Generic]

Canada¾5 mg (Rx)[Adalat]

10 mg (Rx)[Adalat] [Apo-Nifed] [Novo-Nifedin] [Nu-Nifed]

Packaging and storage:

Store between 15 and 25 °C (59 and 77 °F), unless otherwise specified by manufacturer. Store in a tight, light-resistant container.

Auxiliary labeling:

· Do not take other medicines without physician's advice.

Note: Check refill frequency to determine compliance in hypertensive patients.

NIFEDIPINE EXTENDED-RELEASE TABLETS

Usual adult and adolescent dose

Antianginal¾Adalat XL or Procardia XL¾

Oral, 30 or 60 mg once a day, the dosage being adjusted over a seven- to fourteen-day period as needed and tolerated 196, 222, 223.

Antihypertensive¾Adalat CC¾

Initial¾Oral, 30 mg once a day 220.

Maintenance¾Oral, 30 to 60 mg once a day, the dosage being adjusted over a seven- to fourteen-day period as needed and tolerated 220.

Note:

Adalat CC should be taken on an empty stomach 220.

Adalat PA¾

Initial¾Oral, 10 or 20 mg two times a day 221.

The full antihypertensive effect may not be apparent for three weeks; therefore, a dosage increase, if needed, should occur at three-week intervals 221.

Maintenance¾Oral, 20 mg two times a day 221.

Note:

Geriatric patients may be more sensitive to the effects of the usual adult dose.

Adalat XL¾

Initial¾Oral, 30 or 60 mg once a day, the dosage being adjusted over a seven- to fourteen-day period as needed and tolerated 222.

Maintenance¾Oral, 60 to 90 mg once daily 222.

Procardia XL¾

Oral, 30 or 60 mg once a day, the dosage being adjusted over a seven- to fourteen-day period as needed and tolerated 223

Usual adult prescribing limits

Antianginal

90 mg a day (Adalat XL, Procardia XL) 222, 223.

Antihypertensive

90 mg a day (Adalat CC) 220 , or 80 mg a day (Adalat PA) 221 , or 120 mg a day (Adalat XL, Procardia XL) 222, 223

Usual pediatric dose

Dosage has not been established.

Strength(s) usually available

U.S.¾30 mg (Rx)[Adalat CC] [Procardia XL]

60 mg (Rx)[Adalat CC] [Procardia XL]

90 mg (Rx)[Adalat CC] [Procardia XL]

Canada¾10 mg[Adalat PA]

20 mg[Adalat PA]

30 mg[Adalat XL]

60 mg[Adalat XL]

Note: Although similar in appearance to conventional tablets, Adalat XL and Procardia XL consist of an osmotically active drug core surrounded by a semipermeable membrane which is designed to release nifedipine at a constant rate over 24 hours; following the release of the drug, the insoluble tablet shell is eliminated in the feces 222, 223.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a well-closed container, unless otherwise specified by manufacturer.

Auxiliary labeling:

· Do not take other medicines without physician's advice.Adalat CC
· Do not take other medicines without physician's advice.
· Take on empty stomach.

Note: Check refill frequency to determine compliance in hypertensive patients.

NIMODIPINE

Summary of Differences

Indications¾
Indicated for treatment of subarachnoid hemorrhage-associated neurologic deficits.

Pharmacology/pharmacokinetics¾
Dihydropyridine structure.
Potent peripheral vasodilator; does not depress sinoatrial (SA) or atrioventricular (AV) node; no negative inotropic effect; reflex increase in heart rate in response to vasodilation occurs.

Cerebroselective.

Side/adverse effects¾

Differences in frequencies are due to differences in pharmacological effects. Also causes thrombocytopenia (rare).

Oral Dosage Forms

NIMODIPINE CAPSULES

Usual adult dose

Subarachnoid hemorrhage-associated neurologic deficits¾Oral, 60 mg every four hours 140, 142, 153 , beginning within ninety-six hours after the subarachnoid hemorrhage and continuing for twenty-one days 140, 144, 146, 153.

Note: In patients with hepatic function impairment, dosage should be reduced to 30 mg every four hours, with close monitoring of blood pressure and heart rate 140.

Geriatric patients may be more sensitive to the effects of the usual adult dose 147, 149.

Usual pediatric dose

Dosage has not been established.

Strength(s) usually available

U.S.¾30 mg (Rx)[Nimotop]

Canada¾30 mg (Rx)[Nimotop]

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F) 140 , in a well-closed container, unless otherwise specified by manufacturer. Protect from light 140.

Protect from freezing 140.

Preparation of dosage form:

For patients who cannot take oral solids¾

For patients who cannot swallow, a hole may be made in both ends of the capsule with an 18 gauge needle and the contents of the capsule withdrawn into a syringe, and then emptied into the patient's nasogastric tube and washed down the tube with 30 mL of 0.9% sodium chloride solution 140.

VERAPAMIL

Summary of Differences

Indications¾

Indicated for treatment of supraventricular tachyarrhythmias; oral dosage form indicated for prophylaxis.

Also used to treat hypertrophic cardiomyopathy.

Pharmacology/pharmacokinetics¾

Diphenylalkylamine structure.

Depresses sinoatrial (SA) and atrioventricular (AV) nodes; usually does not significantly alter heart rate but may cause bradycardia; negative inotropic effect countered by reduction in afterload.

Precautions¾

Pediatrics¾In rare instances, severe adverse hemodynamic effects have occurred after intravenous administration of verapamil in neonates and infants.

Laboratory value alterations¾Prolongs P-R interval in serum concentrations greater than 30 nanograms per mL.

Medical considerations/contraindications¾Contraindicated in patients with second- or third-degree atrioventricular (AV) block, sinoatrial (SA) nodal function impairment, or Wolff-Parkinson-White or Lown-Ganong-Levine syndrome accompanied by atrial flutter or fibrillation, except in patients with a functioning artificial ventricular pacemaker. Caution necessary in patients with neuromuscular transmission deficiency, and wide-complex ventricular tachycardia (with intravenous use).

Side/adverse effects¾

Differences in frequencies are due to differences in pharmacological effects.

Additional Dosing Information

See also General Dosing Information .

Dermatologic side effects usually disappear even with continued use. However, if skin eruptions persist, it is recommended that verapamil therapy be withdrawn, since progression to erythema multiforme has been reported rarely 76.

For parenteral dosage forms only

Parenteral dosage is indicated in the management of cardiac arrhythmias with close monitoring. Emergency equipment and medications should be readily available.

Oral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling.

VERAPAMIL TABLETS USP

Note: The dosing and strengths of verapamil are expressed in terms of hydrochloride salt.

Usual adult and adolescent 80 dose

Antianginal
Antiarrhythmic
Antihypertensive or *

[Hypertrophic cardiomyopathy therapy adjunct]¾Oral, initially 80 to 120 mg (HCl) three times a day, the dosage being increased at daily or weekly intervals as needed and tolerated 169, 180.

Note: An initial dose of 40 mg (HCl) three times a day is recommended in patients who may have an increased response to verapamil (e.g., those with hepatic function impairment, elderly patients 169, 180 , patients with poor left ventricular function 104).

The total daily dose usually ranges from 240 to 480 mg.

Because of prolongation of the half-life with repeated dosing, decreased frequency of dosing may be possible; dosage should be individualized. 3

Geriatric patients may be more sensitive to the effects of the usual adult dose.

Usual adult prescribing limits

480 mg (HCl) daily in divided doses 180 ; has been used in doses up to 720 mg per day in the treatment of hypertrophic cardiomyopathy.

Usual pediatric dose

For infants less than 1 year and children 1 to 15 years of age¾Oral, 4 to 8 mg (HCl) per kg of body weight per day in divided doses 105.

Usual geriatric dose

Oral, initially 40 mg (HCl) three times a day, the dosage being adjusted as needed and tolerated 81, 169.

Strength(s) usually available

U.S.¾40 mg (HCl) (Rx)[Calan] [Isoptin (scored)] [Generic]

80 mg (HCl) (Rx)[Calan (scored)] [Isoptin (scored)] [Generic]

120 mg (HCl) (Rx)[Calan (scored)] [Isoptin (scored)] [Generic]

Canada¾80 mg (HCl) (Rx)[Apo-Verap] [Isoptin] [Novo-Veramil] [Nu-Verap] [Generic]

120 mg (HCl) (Rx)[Apo-Verap] [Isoptin] [Novo-Veramil] [Nu-Verap] [Generic]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container. Protect from light.

Auxiliary labeling:

· Do not take other medicines without physician's advice.

Note: Check refill frequency to determine compliance in hypertensive patients.

VERAPAMIL HYDROCHLORIDE EXTENDED-RELEASE CAPSULES

Usual adult and adolescent dose

Antihypertensive¾Oral, initially 240 mg once a day, the dosage being increased in increments of 120 mg per day at daily or weekly intervals as needed and tolerated 202.

Note: An initial dose of 120 mg per day is recommended in patients who may have an increased response to verapamil (e.g., elderly, small people, etc.) 201.

The total daily dose usually ranges from 240 to 480 mg.

Geriatric patients may be more sensitive to the effects of the usual adult dose.

Usual pediatric dose

Dosage has not been established.

Strength(s) usually available

U.S.¾120 mg (Rx)[Verelan]

180 mg (Rx)[Verelan]

240 mg (Rx)[Verelan]

360 mg (Rx)[Verelan]

Canada¾120 mg (Rx)[Verelan]

180 mg (Rx)[Verelan]

240 mg (Rx)[Verelan]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container 201.

Protect from light 201.

Auxiliary labeling:

· Do not take other medicines without physician's advice.

Note: Check refill frequency to determine compliance in hypertensive patients.

VERAPAMIL HYDROCHLORIDE EXTENDED-RELEASE TABLETS

Usual adult and adolescent 80 dose

Antihypertensive¾Oral, initially 180 mg once a day in the morning with food, the dosage being increased at daily or weekly intervals as needed and tolerated in the following order: 240 mg once a day in the morning; 180 mg every twelve hours or 240 mg in the morning and 120 mg in the evening; 240 mg every twelve hours 187.

Note: Lower initial doses (e.g., 120 mg per day) may be necessary in patients with a potential increased response to verapamil 187.

Calan SR and Isoptin SR 240 mg tablets may be broken in half, but should not be crushed or chewed 175.

Geriatric patients may be more sensitive to the effects of the usual adult dose.

Usual pediatric dose

Dosage has not been established.

Strength(s) usually available

U.S.¾120 mg (Rx)[Calan SR] [Isoptin SR]

180 mg (Rx)[Calan SR] [Isoptin SR]

240 mg (Rx)[Calan SR (scored)] [Isoptin SR (scored)]

Canada¾120 mg (Rx)[Isoptin SR]

180 mg (Rx)[Isoptin SR]

240 mg (Rx)[Isoptin SR (scored)]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight, light-resistant container 187.

Auxiliary labeling:

· Take with meals or milk.
· Do not take other medicines without physician's advice.

Note: Check refill frequency to determine compliance in hypertensive patients.

Parenteral Dosage Forms

VERAPAMIL INJECTION USP

Note: The dosing and strengths of verapamil are expressed in terms of hydrochloride salt.

Usual adult dose

Intravenous, initially 5 to 10 mg (HCl) (or 75 to 150 mcg [0.075 to 0.15 mg] per kg of body weight) administered slowly over a two-minute period with continuous ECG and blood pressure monitoring 173.

If response is not adequate, 10 mg (or 150 mcg [0.15 mg] per kg of body weight) may be administered thirty minutes after completion of initial dose.

Note: In geriatric patients, the intravenous dose should be administered slowly over a three-minute period to minimize undesired effects 183.

Usual pediatric dose

The following doses should be administered slowly over a two-minute period, with continuous ECG monitoring. If response is not adequate, a repeat dose may be administered thirty minutes after completion of initial dose.

Infants up to 1 year of age¾Initially, 100 to 200 mcg (HCl) (0.1 to 0.2 mg) per kg of body weight (usual single dose range, 0.75 to 2 mg).

Children 1 to 15 years of age¾Initially, 100 to 300 mcg (HCl) (0.1 to 0.3 mg) per kg of body weight (usual single dose range, 2 to 5 mg) not to exceed a total of 5 mg. For repeat dose, thirty minutes after initial dose, do not exceed 10 mg as a single dose.

Strength(s) usually available

U.S.¾2.5 mg (HCl) per mL (Rx)[Isoptin] [Generic] (sodium chloride 8.5 mg per mL)

Canada¾2.5 mg (HCl) per mL (Rx)[Isoptin] [Generic]

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from light. Protect from freezing.

Stability:

Verapamil hydrochloride injection is physically and chemically compatible with Ringer's injection or 5% dextrose or 0.9% sodium chloride injection.

Incompatibilities:

Verapamil hydrochloride injection is physically incompatible with albumin, amphotericin B injection, hydralazine hydrochloride injection, and sulfamethoxazole and trimethoprim injection 29, 173.

Precipitation of verapamil hydrochloride will occur in any solution with a pH greater than 6 173.

.