CARDENE® SR

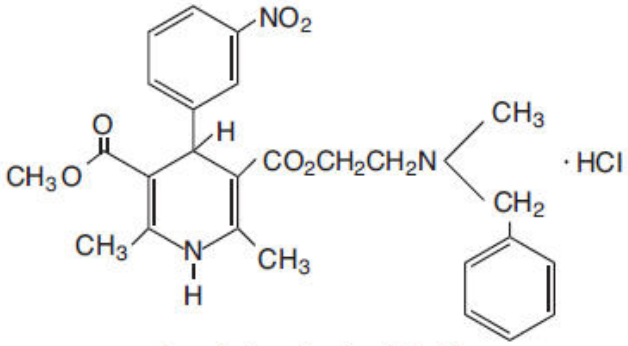
(nicardipine hydrochloride)

SUSTAINED RELEASE CAPSULES

DESCRIPTION

CARDENE® SR is a sustained release formulation of CARDENE®. Cardene SR capsules for oral administration each contain 30 mg, 45 mg or 60 mg of nicardipine hydrochloride. Nicardipine hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium entry blocker).

Nicardipine hydrochloride is a dihydropyridine derivative with the IUPAC (International Union of Pure and Applied Chemistry) chemical name (±)-2-(benzyl-methyl amino) ethyl methyl 1,4-dihydro-2,6 dimethyl-4-(m-nitrophenyl)-3, 5-pyridinedicarboxylate monohydrochloride, and it has the following structure:



nicardipine hydrochloride

Nicardipine hydrochloride is a greenish-yellow, odorless, crystalline powder that melts at about 169°C. It is freely soluble in chloroform, methanol and glacial acetic acid, sparingly soluble in anhydrous ethanol, slightly soluble in n-butanol, water, 0.01 M potassium dihydrogen phosphate, acetone and dioxane, very slightly soluble in ethyl acetate, and practically insoluble in benzene, ether and hexane. It has a molecular weight of 515.99.

Cardene SR is available in hard gelatin capsules containing 30 mg, 45 mg or 60 mg nicardipine hydrochloride. All strengths contain a two component capsule fill. A powder component containing 25% of total nicardipine hydrochloride dose contains pregelatinized starch and magnesium stearate as inactive ingredients. A spherical granule component containing 75% of total nicardipine hydrochloride dose also contains microcrystalline cellulose, starch, lactose and methacrylic acid copolymer Type C as inactive ingredients.

The colorants used in the 30-mg capsules are titanium dioxide, FD&C Red No. 40 and red iron oxide, and the colorants used in the 45-mg and 60-mg capsule are titanium dioxide and FD&C Blue No. 2.

CLINICAL PHARMACOLOGY

Mechanism of Action

Nicardipine is a calcium entry blocker (slow channel blocker or calcium ion antagonist) that inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle without changing serum calcium concentrations. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. The effects of nicardipine are more selective to vascular smooth muscle than cardiac muscle. In animal models, nicardipine produces relaxation of coronary vascular smooth muscle at drug levels that cause little or no negative inotropic effect.

Pharmacokinetics and Metabolism

Nicardipine is completely absorbed following oral doses administered as capsules, and the systemic bioavailability is about 35% following a 30-mg oral dose at steady-state. The pharmacokinetics of nicardipine are nonlinear due to saturable hepatic first-pass metabolism.

Following oral administration of Cardene SR, plasma levels are detectable as early as 20 minutes and maximal plasma levels are achieved as a broad peak generally between 1 and 4 hours. The average terminal plasma half-life of nicardipine is 8.6 hours. Following oral administration increasing doses result in disproportionate increases in plasma levels. Steady-state C_{max} values following 30-, 45- and 60-mg doses every 12 hours averaged 13.4, 34.0, and 58.4 ng/mL, respectively. Hence, increasing the dose twofold increases maximum plasma levels 4-fold to 5-fold. A similar disproportionate increase is observed with AUC. In comparison with equivalent daily doses of CARDENE capsules, Cardene SR shows a significant reduction in C_{max}. Cardene SR also has somewhat lower bioavailability than CARDENE except at the highest dose. Minimum plasma levels produced by equivalent daily doses are similar. Cardene SR thus exhibits significantly reduced fluctuation in plasma levels in comparison to CARDENE capsules.

When Cardene SR was administered with a high-fat breakfast, mean C_{max} was 45% lower, AUC was 25% lower and trough levels were 75% higher than when Cardene SR was given in the fasting state. Thus, taking Cardene SR with the meal reduced the fluctuation in plasma levels. Clinical trials establishing the safety and efficacy of CARDENE SR were carried out in patients without regard to the timing of meals.

Nicardipine is highly protein bound (>95%) in human plasma over a wide concentration range.

Nicardipine is metabolized extensively by the hepatic cytochrome P450 enzymes, CYP2C8, 2D6, and 3A4; less than 1% of intact drug is detected in the urine. Following a radioactive oral dose in solution, 60% of the radioactivity was recovered in the urine and 35% in feces. Most of the dose (over 90%) was recovered within 48 hours of dosing. Nicardipine does not induce its own metabolism, however, nicardipine causes inhibition of certain cytochrome P450 enzymes (including CYP3A4, CYP2D6, CYP2C8, and CYP2C19). Inhibition of these enzymes may result in increased plasma levels of certain drugs, including cyclosporine and tacrolimus (see Drug Interactions). The altered pharmacokinetics may necessitate dosage adjustment of the affected drug or discontinuation of treatment.

Nicardipine plasma levels following administration of Cardene SR in hypertensive patients with moderate renal impairment (creatinine clearance 10 to 55 mL/min) were significantly higher following a single-oral dose and at steady-state than in hypertensive patients with mildly impaired renal function (creatinine clearance >55 mL/min). After 45-mg Cardene SR bid at steady-state, C_{max} and AUC were 2-fold to 3-fold higher in the patients with moderate renal impairment. Plasma levels in patients with mildly impaired renal function were similar to those in normal subjects.

In patients with severe renal impairment undergoing routine hemodialysis, plasma levels following a single dose of Cardene SR were not significantly different from those patients with mildly impaired renal function.

Because nicardipine is extensively metabolized by the liver, the plasma levels of the drug are influenced by changes in hepatic function. Following administration of CARDENE capsules, nicardipine plasma levels were higher in patients with severe liver disease (hepatic cirrhosis confirmed by liver biopsy or presence of endoscopically-confirmed esophageal varices) than in normal subjects. After 20-mg CARDENE bid at steady-state, C_{max} and AUC were 1.8-fold and 4-fold higher, and the terminal half-life was prolonged to 19 hours in these patients. Cardene SR has not been studied in patients with severe liver disease.

Geriatric Pharmacokinetics

The pharmacokinetics of Cardene SR in elderly hypertensive subjects (mean age 70 years) were compared to those in younger hypertensive subjects (mean age 44 years). After a single dose and after 1 week of dosing with Cardene SR there were no significant differences in C_{max}, T_{max}, AUC or clearance between the young and elderly subjects. In both groups of subjects, steady-state plasma levels were significantly higher than following a single dose. In the elderly subjects, a disproportional increase in plasma levels with dose was observed similar to that observed in normal subjects.

Hemodynamics

In man, nicardipine produces a significant decrease in systemic vascular resistance. The degree of vasodilation and the resultant hypotensive effects are more prominent in hypertensive patients. In hypertensive patients, nicardipine reduces the blood pressure at rest and during isometric and dynamic exercise. In normotensive patients, a small decrease of about 9 mm Hg in systolic and 7 mm Hg in diastolic blood pressure may accompany this fall in peripheral resistance. An increase in heart rate may occur in response to the vasodilation and decrease in blood pressure, and in a few patients this heart rate increase may be pronounced. In clinical studies mean heart rate at time of peak plasma levels was usually increased by 5 to 10 beats per minute compared to placebo, with the greater increases at higher doses, while there was no difference from placebo at the end of the dosing interval. Hemodynamic studies following intravenous dosing in patients with coronary artery disease and normal or moderately abnormal left ventricular function have shown significant increases in ejection fraction and cardiac output with no significant change, or a small decrease, in left ventricular end-diastolic pressure (LVEDP). Although there is evidence that nicardipine increases coronary blood flow, there is no evidence that this property plays any role in its effectiveness in stable angina. In patients with coronary artery disease, intracoronary administration of nicardipine caused no direct myocardial depression. CARDENE does,

however, have a negative inotropic effect in some patients with severe left ventricular dysfunction and could, in patients with very impaired function, lead to worsened failure.

"Coronary Steal," the detrimental redistribution of coronary blood flow in patients with coronary artery disease (diversion of blood from under-perfused areas toward better perfused areas), has not been observed during nicardipine treatment. On the contrary, nicardipine has been shown to improve systolic shortening in normal and hypokinetic segments of myocardial muscle, and radionuclide angiography has confirmed that wall motion remained improved during an increase in oxygen demand. Nonetheless, occasional patients have developed increased angina upon receiving nicardipine. Whether this represents steal in those patients, or is the result of increased heart rate and decreased diastolic pressure, is not clear.

In patients with coronary artery disease nicardipine improves L.V. diastolic distensibility during the early filling phase, probably due to a faster rate of myocardial relaxation in previously under-perfused areas. There is little or no effect on normal myocardium, suggesting the improvement is mainly by indirect mechanisms such as afterload reduction and reduced ischemia. Nicardipine has no negative effect on myocardial relaxation at therapeutic doses. The clinical consequences of these properties are as yet undemonstrated.

Electrophysiologic Effects

In general, no detrimental effects on the cardiac conduction system were seen with the use of CARDENE.

Nicardipine increased the heart rate when given intravenously during acute electrophysiologic studies and prolonged the corrected QT interval to a minor degree. The sinus node recovery times and SA conduction times were not affected by the drug. The PA, AH and HV intervals* and the functional and effective refractory periods of the atrium were not prolonged by nicardipine and the relative and effective refractory periods of the His-Purkinje system were slightly shortened after intravenous nicardipine.

Renal Function

There is a transient increase in electrolyte excretion, including sodium. CARDENE does not cause generalized fluid retention, as measured by weight changes.

*PA=conduction time from high to low right atrium, AH=conduction time from low right atrium to His bundle deflection or AV nodal conduction time, HV=conduction time through the His bundle and the bundle branch-Purkinje system.

Effects in Hypertension

Cardene SR produced decreases in both systolic and diastolic blood pressure throughout the dosing interval in clinical trials. The antihypertensive efficacy of Cardene SR administered twice daily has been

demonstrated using in-clinic blood pressure measures in placebo-controlled trials involving patients with mild to moderate hypertension and in trials using 12 or 24 hour ambulatory blood pressure monitoring.

INDICATIONS AND USAGE

Cardene SR is indicated for the treatment of hypertension. CARDENE SR may be used alone or in combination with other anti-hypertensive drugs.

CONTRAINDICATIONS

CARDENE is contraindicated in patients with hypersensitivity to the drug.

Because part of the effect of CARDENE is secondary to reduced afterload, the drug is also contraindicated in patients with advanced aortic stenosis. Reduction of diastolic pressure by any means in these patients may worsen rather than improve myocardial oxygen balance.

WARNINGS

Increased Angina in Patients With Angina

In short-term, placebo-controlled angina trials with CARDENE (an immediate release oral dosage form of nicardipine), about 7% of patients on CARDENE (compared with 4% of patients on placebo) have developed increased frequency, duration or severity of angina. Comparisons with beta-blockers also show a greater frequency of increased angina, 4% vs 1%. The mechanism of this effect has not been established.

Use in Patients With Congestive Heart Failure

Although preliminary hemodynamic studies in patients with congestive heart failure have shown that CARDENE reduced afterload without impairing myocardial contractility, it has a negative inotropic effect in vitro and in some patients. Caution should be exercised when using the drug in congestive heart failure patients, particularly in combination with a beta-blocker.

Beta-Blocker Withdrawal

CARDENE is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker, preferably over 8 to 10 days.

PRECAUTIONS

General

Blood Pressure: Because CARDENE decreases peripheral resistance, careful monitoring of blood pressure during the initial administration and titration of CARDENE is suggested. CARDENE, like other calcium channel blockers, may occasionally produce symptomatic hypotension. Caution is advised to avoid

systemic hypotension when administering the drug to patients who have sustained an acute cerebral infarction or hemorrhage.

Use in Patients With Impaired Hepatic Function: Since the liver is the major site of biotransformation and since CARDENE is subject to first-pass metabolism, CARDENE should be used with caution in patients having impaired liver function or reduced hepatic blood flow. Patients with severe liver disease developed elevated blood levels (fourfold increase in AUC) and prolonged half-life (19 hours) of CARDENE.

Use in Patients With Impaired Renal Function: When 45-mg CARDENE SR bid was given to hypertensive patients with moderate renal impairment, mean AUC and C_{max} values were approximately 2-fold to 3-fold higher than in patients with mild renal impairment. Doses in these patients must be adjusted. Mean AUC and C_{max} values were similar in patients with mildly impaired renal function and normal volunteers (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Drug Interactions

Beta-Blockers: In controlled clinical studies, adrenergic beta-receptor blockers have been frequently administered concomitantly with CARDENE. The combination is well tolerated.

Cimetidine: Cimetidine increases CARDENE plasma levels. Patients receiving the two drugs concomitantly should be carefully monitored.

Digoxin: Some calcium blockers may increase the concentration of digitalis preparations in the blood. CARDENE usually does not alter the plasma levels of digoxin; however, serum digoxin levels should be evaluated after concomitant therapy with CARDENE is initiated.

Fentanyl Anesthesia: Severe hypotension has been reported during fentanyl anesthesia with concomitant use of a beta-blocker and a calcium channel blocker. Even though such interactions were not seen during clinical studies with CARDENE, an increased volume of circulating fluids might be required if such an interaction were to occur.

Cyclosporine: Concomitant administration of oral or intravenous nicardipine and cyclosporine results in elevated plasma cyclosporine levels through nicardipine inhibition of hepatic microsomal enzymes, including CYP3A4. Plasma concentrations of cyclosporine should therefore be closely monitored, and its dosage reduced accordingly, in patients treated with nicardipine.

Tacrolimus: Concomitant administration of oral or intravenous nicardipine and tacrolimus may result in elevated plasma tacrolimus levels through nicardipine inhibition of hepatic microsomal enzymes, including CYP3A4. Closely monitor plasma concentrations of tacrolimus during nicardipine administration, and adjust the dose of tacrolimus accordingly.

When therapeutic concentrations of furosemide, propranolol, dipyridamole, warfarin, quinidine or naproxen were added to human plasma (in vitro), the plasma protein binding of CARDENE was not altered.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Rats treated with nicardipine in the diet (at concentrations calculated to provide daily dosage levels of 5, 15 or 45 mg/kg/day) for 2 years showed a dose-dependent increase in thyroid hyperplasia and neoplasia (follicular adenoma/carcinoma). One- and 3-month studies in the rat have suggested that these results are linked to a nicardipine-induced reduction in plasma thyroxine (T4) levels with a consequent increase in plasma levels of thyroid stimulating hormone (TSH). Chronic elevation of TSH is known to cause hyperstimulation of the thyroid. In rats on an iodine deficient diet, nicardipine administration for 1 month was associated with thyroid hyperplasia that was prevented by T4 supplementation. Mice treated with nicardipine in the diet (at concentrations calculated to provide daily dosage levels of up to 100 mg/kg/day) for up to 18 months showed no evidence of neoplasia of any tissue and no evidence of thyroid changes. There was no evidence of thyroid pathology in dogs treated with up to 25 mg nicardipine/kg/day for 1 year and no evidence of effects of nicardipine on thyroid function (plasma T4 and TSH) in man.

There was no evidence of a mutagenic potential of nicardipine 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.

No impairment of fertility was seen in male or female rats administered nicardipine at oral doses as high as 100 mg/kg/day (50 times the maximum recommended daily dose in man, assuming a patient weight of 60 kg).

Pregnancy

Pregnancy Category C. Nicardipine was embryocidal when administered orally to pregnant Japanese White rabbits, during organogenesis, at 150 mg/kg/day (a dose associated with marked body weight gain suppression in the treated doe) but not at 50 mg/kg/day (25 times the maximum recommended dose in man). No adverse effects on the fetus were observed when New Zealand albino rabbits were treated, during organogenesis, with up to 100 mg nicardipine/kg/day (a dose associated with significant mortality in the treated doe). In pregnant rats administered nicardipine orally at up to 100 mg/kg/day (50 times the maximum recommended human dose) there was no evidence of embryolethality or teratogenicity. However, dystocia, reduced birth weights, reduced neonatal survival and reduced neonatal weight gain were noted. There are no adequate and well-controlled studies in pregnant women. Cardene SR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Studies in rats have shown significant concentrations of nicardipine in maternal milk following oral administration. For this reason it is recommended that women who wish to breastfeed should not take this drug.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Pharmacokinetic parameters did not differ significantly between elderly hypertensive subjects (mean age: 70 years) and younger hypertensive subjects (mean age: 44 years) after 1 week of treatment with CARDENE SR (see CLINICAL PHARMACOLOGY: Geriatric Pharmacokinetics).

Clinical studies of nicardipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE EVENTS

In multiple-dose US and foreign controlled studies, 667 patients received Cardene SR. In these studies adverse events were elicited by non-directed and in some cases directed questioning; adverse events were generally not serious and about 9% of patients withdrew prematurely from the studies because of them.

Hypertension

The incidence rates of adverse events in hypertensive patients were derived from placebo-controlled clinical trials. Following are the rates of adverse events for Cardene SR (n=322) and placebo (n=140), respectively, that occurred in 0.6% of patients or more on CARDENE SR. These represent events considered probably drug related by the investigator. Where the frequency of adverse events for Cardene SR and placebo is similar, causal relationship is uncertain. The only dose-related effect was pedal edema.

Percentage of Patients With Probably Drug Related Adverse Events in Placebo-Controlled Studies

Adverse Event	**Cardene SR (n=322)**	**Placebo (n=140)**
Headache	6.2	7.1
Pedal Edema	5.9	1.4
Vasodilatation	4.7	1.4
Palpitation	2.8	1.4

Nausea	1.9	0.7
Dizziness	1.6	0.7
Asthenia	0.9	0.7
Postural Hypotension	0.9	0
Increased UrinaryFrequency	0.6	0
Pain	0.6	0
Rash	0.6	0
Sweating Increased	0.6	0
Vomiting	0.6	0

Incidence (%) of Discontinuations Due to Any Adverse Event in Placebo-Controlled Studies

Adverse Event	**Cardene SR (n=322)**	**Placebo (n=140)**
Headache	2.5	1.4
Palpitation	2.2	0.7
Dizziness	1.9	0.7
Asthenia	1.9	0
Pedal Edema	1.2	0
Nausea	1.2	0

Rash	0.9	0.7
Diarrhea	0.9	0
Tachycardia	0.9	0
Blurred Vision	0.6	0
Chest Pain	0.6	0
Face Edema	0.6	0
Myocardial Infarct	0.6	0
Vasodilatation	0.6	0
Vomiting	0.6	0

Uncontrolled experience in over 300 patients with hypertension treated for up to 27.5 months with Cardene SR has shown no unexpected adverse events or increase in incidence of adverse events compared to the controlled clinical trials.

Rare Events

The following rare adverse events have been reported in clinical trials or the literature:

Body as a Whole: infection, allergic reaction

Cardiovascular: hypotension, atypical chest pain, peripheral vascular disorder, ventricular extrasystoles, ventricular tachycardia, angina pectoris

Digestive: sore throat, abnormal liver chemistries

Musculoskeletal: arthralgia

Nervous: hot flashes, vertigo, hyperkinesia, impotence, depression, confusion, anxiety

Respiratory: rhinitis, sinusitis

Special Senses: tinnitus, abnormal vision, blurred vision

Angina

Data are available from only 91 patients with chronic stable angina pectoris who received Cardene SR 30 to 60 mg administered twice daily in open-label clinical trials. Fifty-eight of these patients were treated for at least 30 days. The four most frequently reported adverse events thought by the investigators to be probably related to the use of Cardene SR were vasodilatation (5.5%), pedal edema (4.4%), asthenia (4.4%), and dizziness (3.3%).

OVERDOSAGE

Three overdosages with CARDENE or Cardene SR have been reported. Two occurred in adults, 1 of whom ingested 600 mg of CARDENE and the other 2160 mg of Cardene SR. Symptoms included marked hypotension, bradycardia, palpitations, flushing, drowsiness, confusion, and slurred speech. All symptoms resolved without sequelae. The third over-dosage occurred in a 1-year-old child who ingested half of the powder in a 30-mg CARDENE capsule. The child remained asymptomatic.

Based on results obtained in laboratory animals, overdosage may cause systemic hypotension, bradycardia (following initial tachycardia) and progressive atrioventricular conduction block. Reversible hepatic function abnormalities and sporadic focal hepatic necrosis were noted in some animal species receiving very large doses of nicardipine.

For treatment of overdose standard measures (for example, evacuation of gastric contents, elevation of extremities, attention to circulating fluid volume, and urine output) including monitoring of cardiac and respiratory functions should be implemented. The patient should be positioned so as to avoid cerebral anoxia. Frequent blood pressure determinations are essential. Vasopressors are clinically indicated for patients exhibiting profound hypotension. Intravenous calcium gluconate may help reverse the effects of calcium entry blockade.

DOSAGE AND ADMINISTRATION

The dose of Cardene SR should be individually adjusted according to the blood pressure response beginning with 30 mg two times daily. The effective doses in clinical trials have ranged from 30 mg to 60 mg two times daily. The maximum blood pressure lowering effect at steady-state is sustained from 2 hours until 6 hours after dosing.

When initiating therapy or upon increasing dose, blood pressure should be measured 2 to 4 hours after the first dose or dose increase, as well as at the end of a dosing interval.

The total daily dose of immediate release nicardipine (CARDENE) may not be a useful guide to judging the effective dose of Cardene SR. Patients currently receiving immediate release nicardipine may be

titrated with Cardene SR starting at their current total daily dose of immediate release nicardipine and then reexamined to assess the adequacy of blood pressure control.

Concomitant Use With Other Antihypertensive Agents:

1. Diuretics: CARDENE may be safely coadministered with thiazide diuretics.

2. Beta-Blockers: CARDENE may be safely coadministered with beta-blockers (see Drug Interactions).

Special Patient Populations

Renal Insufficiency: Although there is no evidence that CARDENE SR impairs renal function, careful dose titration beginning with 30-mg Cardene SR bid is advised (see PRECAUTIONS).

Hepatic Insufficiency: Cardene SR has not been studied in patients with severe liver impairment (see PRECAUTIONS).

Congestive Heart Failure: Caution is advised when titrating CARDENE SR dosage in patients with congestive heart failure (see WARNINGS).

HOW SUPPLIED

CARDENE® SR 30-mg capsules are available in opaque pink-pink hard gelatin capsules. The capsule cap is printed with Cardene SR 30 mg and the capsule body is printed with EKR Therapeutics, Inc. These are supplied in bottles of 60 (NDC 24477-515-01).

CARDENE® SR 45-mg capsules are available in opaque powder blue-powder blue hard gelatin capsules. The capsule cap is printed with Cardene SR 45 mg and the capsule body is printed with EKR Therapeutics, Inc. These are supplied in bottles of 60 (NDC 24477-517-01).

CARDENE® SR 60-mg capsules are available in opaque light blue-white hard gelatin capsules. The capsule cap is printed with Cardene SR 60 mg and the capsule body is printed with EKR Therapeutics, Inc. These are supplied in bottles of 60 (NDC 24477-516-01).

Store bottles at 15° to 30°C (59° to 86°F) and dispense in light-resistant containers, such as the manufacturer's original container.

For questions of a medical nature or to report an adverse event, call 1-877-207-5802.

U.S. Patent Nos. 4,940,556 and 5,198,226

Cardene® is a registered trademark of EKR Therapeutics, Inc.

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