



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 nicardipine is metabolized in the liver, the drug should be used with caution in patients with impaired liver function or reduced hepatic blood flow. The use of lower dosages should be considered.

Nicardipine administered intravenously has been reported to increase hepatic venous pressure gradient by 4 mmHg in cirrhotic patients at high doses (5 mg/20 min). Cardene I.V. should therefore be used with caution in patients with portal hypertension.

*Use in Patients with Impaired Renal Function:* When Cardene I.V. was given to mild to moderate hypertensive patients with moderate renal impairment, a significantly lower systemic clearance and higher AUC was observed. These results are consistent with those seen after oral administration of nicardipine. Careful dose titration is advised when treating renal impaired patients.

#### DRUG INTERACTIONS

Since Cardene I.V. may be administered to patients already being treated with other medications, including other antihypertensive agents, careful monitoring of these patients is necessary to detect and promptly treat any undesired effects from concomitant administration.

#### BETA-BLOCKERS

In most patients, Cardene I.V. can safely be used concomitantly with beta-blockers. However, caution should be exercised when using Cardene I.V. in combination with a beta-blocker in congestive heart failure patients (see **"Warnings"**). CIMETIDINE

Cimetidine has been shown to increase nicardipine plasma concentrations with Cardene capsule administration. Patients receiving the two drugs concomitantly should be carefully monitored. Data with other histamine-2 antagonists are not available.

#### DIGOXIN

Studies have shown that Cardene capsules usually do not alter digoxin plasma concentrations. However, as a precaution, digoxin levels should be evaluated when concomitant therapy with Cardene I.V. is initiated.

#### FENTANYL ANESTHESIA

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 I.V. (nicardipine hydrochloride), an increased volume of circulating fluids might be required if such an interaction were to occur.

#### CYCLOSPORINE

Concomitant administration of Cardene capsules and cyclosporine results in elevated plasma cyclosporine levels. Plasma concentrations of cyclosporine should therefore be closely monitored during Cardene I.V. administration, and the dose of cyclosporine reduced accordingly.

#### IN VITRO INTERACTION

The plasma protein binding of nicardipine was not altered when therapeutic concentrations of furosemide, propranolol, dipyrnidamole, warfarin, quinidine, or naproxen were added to human plasma *in vitro*.

#### 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 two years showed a dose-dependent increase in thyroid hyperplasia and neoplasia (follicular adenoma/carcinoma). One- and three-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 one 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 one 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 40 mg TID maximum recommended dose in man, assuming a patient weight of 60 kg).

*Pregnancy Category C:* Cardene I.V. at doses up to 5 mg/kg/day to pregnant rats and up to 0.5 mg/kg/day to pregnant rabbits produced no embryotoxicity or teratogenicity. Embryotoxicity was seen at 10 mg/kg/day in rats and at 1 mg/kg/day in rabbits, but no teratogenicity was observed at these doses.

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 embryoletuality 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 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. For this reason, it is recommended that women who wish to breastfeed should not be given this drug.

#### PEDIATRIC USE

Safety and efficacy in patients under the age of 18 have not been established.

#### GERIATRIC USE

The steady-state pharmacokinetics of nicardipine are similar in elderly hypertensive patients (>65 years) and young healthy adults.

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 Experiences

Two hundred forty-four patients participated in two multicenter, double-blind, placebo-controlled trials of Cardene I.V. Adverse experiences were generally not serious and most were expected consequences of vasodilation. Adverse experiences occasionally required dosage adjustment. Therapy was discontinued in approximately 12% of patients, mainly due to hypotension, headache, and tachycardia.

Percent of Patients with Adverse Experiences During the Double-Blind Portion of Controlled Trials		
Adverse Experience	Cardene (n=144)	Placebo (n=100)
<b>Body as a Whole</b>		
Headache	14.6	2.0
Asthenia	0.7	0.0
Abdominal pain	0.7	0.0
Chest pain	0.7	0.0
<b>Cardiovascular</b>		
Hypotension	5.6	1.0
Tachycardia	3.5	0.0
ECG abnormality	1.4	0.0
Postural hypotension	1.4	0.0
Ventricular extrasystoles	1.4	0.0
Extrasystoles	0.7	0.0
Hemopericardium	0.7	0.0
Hypertension	0.7	0.0
Supraventricular tachycardia	0.7	0.0
Syncope	0.7	0.0
Vasodilation	0.7	0.0
Ventricular tachycardia	0.7	0.0
<b>Digestive</b>		
Nausea/vomiting	4.9	1.0
<b>Injection Site</b>		
Injection site reaction	1.4	0.0
Injection site pain	0.7	0.0
<b>Metabolic and Nutritional</b>		
Hypokalemia	0.7	0.0

Manufactured by:  
**Baxter Healthcare Corporation**  
Deerfield, IL 60015 USA

Marketed by:  
**EKR Therapeutics, Inc.**  
Bedminster, NJ 07921 USA

<b>Nervous</b>		
Dizziness	1.4	0.0
Hypesthesia	0.7	0.0
Intracranial hemorrhage	0.7	0.0
Paresthesia	0.7	0.0
<b>Respiratory</b>		
Dyspnea	0.7	0.0
<b>Skin and Appendages</b>		
Sweating	1.4	0.0
<b>Urogenital</b>		
Polyuria	1.4	0.0
Hematuria	0.7	0.0

#### RARE EVENTS

The following rare events have been reported in clinical trials or in the literature in association with the use of intravenously administered nicardipine.

*Body as a Whole:* fever, neck pain

*Cardiovascular:* angina pectoris, atrioventricular block, ST segment depression, inverted T wave, deep-vein thrombophlebitis

*Digestive:* dyspepsia

*Hemic and Lymphatic:* thrombocytopenia

*Metabolic and Nutritional:* hypophosphatemia, peripheral edema

*Nervous:* confusion, hypertonia

*Respiratory:* respiratory disorder

*Special Senses:* conjunctivitis, ear disorder, tinnitus

*Urogenital:* urinary frequency

Sinus node dysfunction and myocardial infarction, which may be due to disease progression, have been seen in patients on chronic therapy with orally administered nicardipine.

#### Overdosage

Several overdosages with orally administered nicardipine have been reported. One adult patient allegedly ingested 600 mg of nicardipine [standard (immediate release) capsules], and another patient, 2160 mg of the sustained release formulation of nicardipine. Symptoms included marked hypotension, bradycardia, palpitations, flushing, drowsiness, confusion and slurred speech. All symptoms resolved without sequelae. An overdosage occurred in a one-year-old child who ingested half of the powder in a 30 mg nicardipine standard capsule. The child remained asymptomatic.

Based on results obtained in laboratory animals, lethal overdose 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 overdosage, standard measures 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

Cardene I.V. (nicardipine hydrochloride) premixed injection is intended for intravenous use. DOSAGE MUST BE INDIVIDUALIZED depending upon the severity of hypertension and the response of the patient during dosing. Blood pressure should be monitored both during and after the infusion; too rapid or excessive reduction in either systolic or diastolic blood pressure during parenteral treatment should be avoided.

#### PREPARATION

Cardene I.V. premixed injection is available as a single use, ready-to-use, iso-osmotic solution for intravenous administration. No further dilution is required. Cardene I.V. premixed injection should not be combined with any product in the same intravenous line or premixed container. Protect from light until ready to use.

Check the GALAXY container for minute leaks prior to use by squeezing the bag firmly. If leaks are found, discard solution as sterility may be impaired. Do not add supplementary medication. Do not use unless solution is clear and seal is intact.

CAUTION: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before the administration of the fluid from the secondary container is complete.

Since the premixed container is for single-use only, any unused portion should be discarded.

*Inspection:* As with all parenteral drugs, Cardene I.V. should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Cardene I.V. is normally a clear, colorless to yellow solution.

#### Preparation for administration:

- Suspend container from eyelet support.
- Remove protector from outlet port at bottom of container.
- Attach administration set. Refer to complete directions accompanying set.

#### DOSAGE

#### As a Substitute for Oral Nicardipine Therapy

The intravenous infusion rate required to produce an average plasma concentration equivalent to a given oral dose at steady state is shown in the following table:

	Oral Cardene Dose	Equivalent I.V. Infusion Rate
	20 mg q8h	0.5 mg/hr
	30 mg q8h	1.2 mg/hr
	40 mg q8h	2.2 mg/hr

#### For Initiation of Therapy in a Drug Free Patient

The time course of blood pressure decrease is dependent on the initial rate of infusion and the frequency of dosage adjustment. Cardene I.V. is administered by slow continuous infusion at a CONCENTRATION OF 0.2 MG/ML. With constant infusion, blood pressure begins to fall within minutes. It reaches about 50% of its ultimate decrease in about 45 minutes and does not reach final steady state for about 50 hours.

When treating acute hypertensive episodes in patients with chronic hypertension, discontinuation of infusion is followed by a 50% offset of action in 30 ± 7 minutes but plasma levels of drug and gradually decreasing antihypertensive effects exist for about 50 hours.

Titration: For gradual reduction in blood pressure, initiate therapy at 25 mL/hr (5.0 mg/hr). If desired blood pressure reduction is not achieved at this dose, the infusion rate may be increased by 12.5 mL/hr (2.5 mg/hr) every 15 minutes up to a maximum of 75 mL/hr (15.0 mg/hr), until desired blood pressure reduction is achieved.

For more rapid blood pressure reduction, initiate therapy at 25 mL/hr (5.0 mg/hr). If desired blood pressure reduction is not achieved at this dose, the infusion rate may be increased by 12.5 mL/hr (2.5 mg/hr) every 5 minutes up to a maximum of 75 mL/hr (15.0 mg/hr), until desired blood pressure reduction is achieved. Following achievement of the blood pressure goal, the infusion rate should be decreased to 15 mL/hr (3.0 mg/hr).

Maintenance: The rate of infusion should be adjusted as needed to maintain desired response.

#### CONDITIONS REQUIRING INFUSION ADJUSTMENT

*Hypotension or Tachycardia:* If there is concern of impending hypotension or tachycardia, the infusion should be discontinued. When blood pressure has stabilized, infusion of Cardene I.V. may be restarted at low doses such as 15 - 25 mL/hr (3.0 - 5.0 mg/hr) and adjusted to maintain desired blood pressure.

*Infusion Site Changes:* Cardene I.V. should be continued as long as blood pressure control is needed. The infusion site should be changed every 12 hours if administered via peripheral vein.

*Impaired Cardiac, Hepatic, or Renal Function:* Caution is advised when titrating Cardene I.V. in patients with congestive heart failure or impaired hepatic or renal function (see **"Precautions"**).

#### TRANSFER TO ORAL ANTIHYPERTENSIVE AGENTS

If treatment includes transfer to an oral antihypertensive agent other than Cardene capsules, therapy should generally be initiated upon discontinuation of Cardene I.V.

If Cardene capsules are to be used, the first dose of a TID regimen should be administered 1 hour prior to discontinuation of the infusion.

#### How Supplied

Cardene I.V. premixed injection is supplied as a single-use, ready-to-use, iso-osmotic solution for intravenous administration in 200 mL GALAXY container (PL2501) with 40 mg (0.2 mg/mL) nicardipine hydrochloride in either dextrose or sodium chloride.

<b>PACK SIZE</b>	<b>DILUENT</b>	<b>NDC NUMBER</b>
10 Bags, each containing 40 mg in 200 mL (0.2 mg/mL)	5% Dextrose	NDC 24477-324-02
10 Bags, each containing 40 mg in 200 mL (0.2 mg/mL)	0.83% Sodium Chloride	NDC 24477-323-02

**Store at controlled room temperature 20° to 25°C (68° to 77°F), refer to USP Controlled Room Temperature.** Protect from freezing. Avoid excessive heat. Protect from light, store in carton until ready to use.

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To report an adverse event, record the lot number and call 1-877-207-5802  
Revised November 2008  
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07-19-58-529 C08-116