

# CARDENE® I.V.

## Premixed Injection (0.2 mg/mL) in either 5% Dextrose or 0.83% Sodium Chloride

71965231

\*BAR CODE LOCATION ONLY

### Rx Only

#### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Cardene I.V. (nicardipine hydrochloride) Premixed Injection safely and effectively. See full prescribing information for Cardene I.V. Premixed Injection (0.2 mg/mL) in either 5% Dextrose or 0.83% Sodium Chloride.

Cardene I.V. Premixed Injection  
Initial U.S. Approval: 1988

#### INDICATIONS AND USAGE

- Cardene I.V. Premixed Injection is a calcium channel blocker indicated for the short-term treatment of hypertension when oral therapy is not feasible.

#### DOSAGE AND ADMINISTRATION

- For Intravenous Use.
- No further dilution is required.
- When substituting for oral nicardipine therapy, use the intravenous infusion rate from the table below (2.1):

Oral Cardene Dose	Equivalent I.V. Infusion Rate
20 mg q8h	0.5 mg/hr = 2.5 mL/hr
30 mg q8h	1.2 mg/hr = 6 mL/hr
40 mg q8h	2.2 mg/hr = 11 mL/hr

- In a patient not receiving oral nicardipine, initiate therapy at 25 mL/hr (5 mg/hr). Increase the infusion rate by 12.5 mL/hr every 5 minutes (for rapid titration) to 15 minutes (for gradual titration) up to a maximum of 75 mL/hr until desired blood pressure reduction is achieved. (2.1)
- If unacceptable hypotension or tachycardia occurs, discontinue the infusion. When blood pressure and heart rate stabilize, restart the infusion at low doses such as 15-25 mL/hr. (2.2)

#### DOSAGE FORMS AND STRENGTHS

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

#### CONTRAINDICATIONS

- Do not use in patients with advanced aortic stenosis (4.1).

#### WARNINGS AND PRECAUTIONS

- Closely monitor response in patients with angina (5.2), heart failure (5.3), impaired hepatic function (5.4), or renal impairment. (5.5)
- To reduce the possibility of venous thrombosis, phlebitis, and vascular impairment, do not use small veins, such as those on the dorsum of the hand or wrist. Exercise extreme care to avoid intra-arterial administration or extravasation. (5.6)
- To minimize the risk of peripheral venous irritation, change the site of infusion of Cardene I.V. Premixed Injection every 12 hours. (5.6)

#### ADVERSE REACTIONS

Most common adverse reactions are headache (15%), hypotension (6%), tachycardia (4%) and nausea/vomiting (5%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact EKR Therapeutics, Inc. at 1-877-207-5802, or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

#### DRUG INTERACTIONS

- Cimetidine increases oral nicardipine plasma levels. (7.2)
- Oral nicardipine increases cyclosporine plasma levels. Monitor cyclosporine levels when co-administering Cardene I.V. Premixed Injection. (7.3)

#### USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data may cause fetal harm. (8.1)
- Nursing mothers: Minimally excreted into human milk. (8.3)
- Safety and efficacy in patients under the age of 18 have not been established. (8.4)

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#### FULL PRESCRIBING INFORMATION

##### 1. INDICATIONS AND USAGE

###### 1.1 Hypertension

Cardene® I.V. (nicardipine hydrochloride) Premixed Injection is indicated for the short-term treatment of hypertension when oral therapy is not feasible or not desirable. For prolonged control of blood pressure, transfer patients to oral medication as soon as their clinical condition permits [*see Dosage and Administration (2.1)*].

##### 2. DOSAGE AND ADMINISTRATION

###### 2.1 Recommended Dosing

Cardene I.V. is intended for intravenous use. Titrate dose to achieve the desired blood pressure reduction. Individualize dosage depending on the blood pressure to be obtained and the response of the patient.

###### 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 = 2.5 mL/hr
30 mg q8h	1.2 mg/hr = 6 mL/hr
40 mg q8h	2.2 mg/hr = 11 mL/hr

###### Dosage for Initiation of Therapy in a Patient Not Receiving Oral Nicardipine

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 (for rapid titration) to 15 minutes (for gradual titration) 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 utilizing rapid titration, decrease the infusion rate to 15 mL/hr (3 mg/hr).

###### Drug Discontinuation and Transition to an Oral Antihypertensive Agent

Discontinuation of infusion is followed by a 50% offset of action in about 30 minutes.

If treatment includes transfer to an oral antihypertensive agent other than oral nicardipine, initiate therapy upon discontinuation of Cardene I.V. Premixed Injection.

If oral nicardipine is to be used, administer the first dose 1 hour prior to discontinuation of the infusion.

###### Special Populations

Titrate Cardene I.V. Premixed Injection slowly in patients with heart failure or impaired hepatic or renal function [*see Warnings and Precautions (5.3, 5.4 and 5.5)*]

###### 2.2 Monitoring

The time course of blood pressure decrease is dependent on the initial rate of infusion and the frequency of dosage adjustment. With constant infusion, blood pressure begins to fall within minutes. It reaches about 50% of its ultimate decrease in about 45 minutes.

Monitor blood pressure and heart rate continually during infusion and avoid too rapid or excessive blood pressure drop during treatment. If there is concern of impending hypotension or tachycardia, the infusion should be discontinued. Then, when blood pressure has stabilized, infusion of Cardene I.V. Premixed Injection 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.

###### 2.3 Instructions for Administration

Administer Cardene I.V. by a central line or through a large peripheral vein. Change the infusion site every 12 hours if administered via peripheral vein [*see Intravenous Infusion Site (5.6)*].

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.

Inspect Cardene I.V. Premixed Injection visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Check the container for minute leaks prior to use by squeezing the bag firmly; ensure that the seal is intact. If leaks are found, discard solution as sterility may be impaired. Cardene I.V. Premixed Injection is normally a clear, colorless to yellow solution.

Do not combine Cardene I.V. Premixed Injection with any product in the same intravenous line or premixed container. Do not add supplementary medication to the bag. Protect from light until ready to use.

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.

###### 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.

##### 3. DOSAGE FORMS AND STRENGTHS

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

##### 4. CONTRAINDICATIONS

###### 4.1 Advanced Aortic Stenosis

Cardene I.V. Premixed Injection is contraindicated in patients with advanced aortic stenosis because part of the effect of Cardene I.V. Premixed Injection is secondary to reduced afterload. Reduction of diastolic pressure in these patients may worsen rather than improve myocardial oxygen balance.

##### 5. WARNINGS AND PRECAUTIONS

###### 5.1 Excessive Pharmacodynamic Effects

In administering nicardipine, close monitoring of blood pressure and heart rate is required. Nicardipine may occasionally produce symptomatic hypotension or tachycardia. Avoid systemic hypotension when administering the drug to patients who have sustained an acute cerebral infarction or hemorrhage.

###### 5.2 Use in Patients with Angina

Increases in frequency, duration, or severity of angina have been seen in chronic therapy with oral nicardipine. Induction or exacerbation of angina has been seen in less than 1% of coronary artery disease patients treated with Cardene I.V. The mechanism of this effect has not been established.

###### 5.3 Use in Patients with Heart Failure

Titrate slowly when using Cardene I.V. Premixed Injection, particularly in combination with a beta-blocker, in patients with heart failure or significant left ventricular dysfunction because of possible negative inotropic effects.

###### 5.4 Use in Patients with Impaired Hepatic Function

Since nicardipine is metabolized in the liver, consider lower dosages and closely monitor responses in patients with impaired liver function or reduced hepatic blood flow.

###### 5.5 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 area under the curve (AUC) was observed. These results are consistent with those seen after oral administration of nicardipine. Titrate gradually in patients with renal impairment.

###### 5.6 Intravenous Infusion Site

To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, extravasation, and the occurrence of vascular impairment, administer drug through large peripheral veins or central veins rather than arteries or small peripheral veins, such as those on the dorsum of the hand or wrist. To minimize the risk of peripheral venous irritation, change the site of the drug infusion every 12 hours.

##### 6. ADVERSE REACTIONS

###### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

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.

The table below shows percentage of patients with adverse events where the rate is >3% more common on Cardene I.V. than placebo.

Adverse Event	Cardene I.V. (N=144)	Placebo (N=100)
<b>Body as a Whole</b>		
Headache, n (%)	21 (15)	2 (2)
<b>Cardiovascular</b>		
Hypotension, n (%)	8 (6)	1 (1)
Tachycardia, n (%)	5 (4)	0
<b>Digestive</b>		
Nausea/vomiting, n (%)	7 (5)	1 (1)

Other adverse 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.

##### 7. DRUG INTERACTIONS

###### 7.1 Beta-Blockers

In most patients, Cardene I.V. Premixed Injection can safely be used concomitantly with beta blockers. However, titrate slowly when using Cardene I.V. Premixed Injection in combination with a beta-blocker in heart failure patients [*see Warnings and Precautions (5.3)*].

###### 7.2 Cimetidine

Cimetidine has been shown to increase nicardipine plasma concentrations with oral nicardipine administration. Frequently monitor response in patients receiving both drugs. Data with other histamine-2 antagonists are not available.

###### 7.3 Cyclosporine

Concomitant administration of oral nicardipine and cyclosporine results in elevated plasma cyclosporine levels. Closely monitor plasma concentrations of cyclosporine during Cardene I.V. Premixed Injection administration, and reduce the dose of cyclosporine accordingly.

###### 7.4 In Vitro Interaction

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

##### 8. USE IN SPECIFIC POPULATIONS

###### 8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of nicardipine use in pregnant women. However, limited human data in pregnant women with preeclampsia or pre-term labor are available. In animal studies, no embryotoxicity occurred in rats with oral doses 8 times the maximum recommended human dose (MRHD) based on body surface area (mg/m<sup>2</sup>), but did occur in rabbits with oral doses at 24 times the maximum recommended human dose (MRHD) based on body surface area (mg/m<sup>2</sup>). Cardene I.V. should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Hypotension, reflex tachycardia, postpartum hemorrhage, tocolysis, headache, nausea, dizziness, and flushing have been reported in pregnant women who were treated with intravenous nicardipine for hypertension during pregnancy. Fetal safety results ranged from transient fetal heart rate decelerations to no adverse events. Neonatal safety data ranged from hypotension to no adverse events.

Adverse events in women treated with intravenous nicardipine during pre-term labor include pulmonary edema, dyspnea, hypoxia, hypotension, tachycardia, headache, and phlebitis at site of injection. Neonatal adverse events include acidosis (pH<7.25).

In embryofetal toxicity studies, nicardipine was administered intravenously to pregnant rats and rabbits during organogenesis at doses up to 0.14 times the MRHD based on body surface area (mg/m<sup>2</sup>) (5 mg/kg/day) (rats) and 0.03 times the MRHD based on body surface area (mg/m<sup>2</sup>) (0.5 mg/kg/day) (rabbits). No embryotoxicity or teratogenicity was seen at these doses. Embryotoxicity, but no teratogenicity was seen at 0.27 times the MRHD based on body surface area (mg/m<sup>2</sup>) (10 mg/kg/day) in rats and at 0.05 times the MRHD based on body surface area (mg/m<sup>2</sup>) (1 mg/kg/day) in rabbits.

In other animal studies, pregnant Japanese White rabbits received oral nicardipine during organogenesis, at doses 8 and 24 times the MRHD based on body surface area (mg/m<sup>2</sup>) (50 and 150 mg/kg/day). Embryotoxicity occurred at the high dose along with signs of maternal toxicity (marked maternal weight gain suppression). New Zealand albino rabbits received oral nicardipine during organogenesis, at doses up to 16 times the MRHD based on body surface area (mg/m<sup>2</sup>) (100 mg nicardipine/kg/day). While significant maternal mortality occurred, no adverse effects on the fetus were observed. Pregnant rats received oral nicardipine from day 6 through day 15 of gestation at doses up to 8 times the MRHD based on body surface area (mg/m<sup>2</sup>) (100 mg/kg/day). There was no evidence of embryotoxicity or teratogenicity; however, dystocia, reduced birth weights, reduced neonatal survival, and reduced neonatal weight gain were noted.

###### 8.3 Nursing Mothers

Nicardipine is minimally excreted into human milk. Among 18 infants exposed to nicardipine through breast milk in the postpartum period, calculated daily infant dose was less than 0.3 mcg and there were no adverse events observed. Consider the possibility of infant exposure when using nicardipine in nursing mothers.

In a study of 11 women who received oral nicardipine 4 to 14 days postpartum, 4 women received immediate-release nicardipine 40 to 80 mg daily, 6 received sustained-release nicardipine 100 to 150 mg daily, and one received intravenous nicardipine 120 mg daily. The peak milk concentration was 7.3 mcg/L (range 1.9-18.8), and the mean milk concentration was 4.4 mcg/L (range 1.3-13.8). Infants received an average of 0.073% of the weight-adjusted maternal oral dose and 0.14% of the weight-adjusted maternal intravenous dose.

In another study of seven women who received intravenous nicardipine for an average of 1.9 days in the immediate postpartum period as therapy for pre-eclampsia, 34 milk samples were obtained at unspecified times and nicardipine was undetectable (<5 mcg/L) in 82% of the samples. Four women who received 1 to 6.5 mg/hour of nicardipine had 6 milk samples with detectable nicardipine levels (range 5.1 to 18.5 mcg/L). The highest concentration of 18.5 mcg/L was found in a woman who received 5.5 mg/hour of nicardipine. The estimated maximum dose in a breastfed infant was < 0.3 mcg daily or between 0.015 to 0.004% of the therapeutic dose in a 1 kg infant.

###### 8.4 Pediatric Use

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

###### 8.5 Geriatric Use

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

Revised: 09/2010

