

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

*APPLICATION NUMBER:*

**019734Orig1s013**

*Trade Name:* CARDENE I.V.

*Generic or Proper Name:* nicardipine hydrochloride

*Sponsor:* Chiesi USA Inc.

*Approval Date:* July 31, 2008

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

# CENTER FOR DRUG EVALUATION AND RESEARCH

## 019734Orig1s013

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**019734Orig1s013**

**APPROVAL LETTER**



NDA 19-734/S-013

EKR Therapeutics, Inc.  
Attention: Mr. Alexander Mironov  
1545 Route 206  
Bedminster, NJ 07921

Dear Mr. Mironov:

Please refer to your supplemental new drug application dated March 31, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cardene (nicardipine hydrochloride) 2.5 mg/mL Intravenous Solution.

We acknowledge receipt of your submissions dated April 25, May 7, and June 12, 2008.

This supplemental new drug application provides for revisions to support the addition of a new container closure system for Cardene I.V. drug product. The proposed new container closure system is a GALAXY® intravenous (IV) bag which contains a concentration of 0.1 mg/mL nicardipine hydrochloride. This application supports two 0.1 mg/mL nicardipine hydrochloride premixed ready-to-use presentations of the currently marketed Cardene IV ampul after dilution.

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the submissions dated March 25 and May 7, 2008.

The final printed labeling (FPL) must be identical to the package insert submitted on March 25, 2008 and the immediate container and carton labels submitted on May 7, 2008. We highly encourage you to submit revised labeling in Physician Labeling Rule (PLR) format. Please refer to the PLR Resource Page at <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for guidance.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved **NDA 19-734/S-013.**"

### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and container labels that are identical to the enclosed inner carton, vial label, inner carton wafer seal and outer carton label as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 19-734/S-013.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

### **PROMOTIONAL MATERIALS**

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

### **LETTERS TO HEALTH CARE PROFESSIONALS**

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH  
Food and Drug Administration  
Suite 12B05  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Alisea Crowley, Pharm.D.  
Regulatory Project Manager  
(301) 796-1144

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.

Director

Division of Cardiovascular and Renal Drug Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Norman Stockbridge  
7/31/2008 03:18:36 PM

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**019734Orig1s013**

**LABELING**

**Cardene® I.V. Premixed Injection (0.1 mg/mL) in either 4.8% Dextrose or 0.86% Sodium Chloride**

**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 (0.1 mg/mL) in either 4.8% Dextrose or 0.86% 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 (2.3):

Oral Cardene Dose	Equivalent I.V. Infusion Rate
20 mg q8h	0.5 mg/hr= 5 mL/hr
30 mg q8h	1.2 mg/hr= 12 mL/hr
40 mg q8h	2.2 mg/hr = 22mL/hr

- In a patient not receiving oral nicardipine, initiate therapy at 50 mL/hr (5 mg/hr). Increase the infusion rate by 25 mL/hr every 5 minutes (for rapid titration) to 15 minutes (for gradual titration) up to a maximum of 150 mL/hr until desired blood pressure reduction is achieved. (2.4)
- If unacceptable hypotension or tachycardia occurs, discontinue the infusion. When blood pressure and heart rate stabilize, restart the infusion at low doses such as 30-50 mL/hr. (2.5)

**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 20 mg (0.1 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 (5.3), heart failure (5.4), impaired hepatic function (5.5), portal hypertension (5.5), or renal impairment (5.6).
- 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. (5.7)
- To minimize the risk of peripheral venous irritation, change the site of infusion of Cardene I.V. Premixed Injection every 12 hours. (5.7)

**ADVERSE REACTIONS**

Most common adverse reactions are headache (14.6%), hypotension (5.6%), tachycardia (3.5%) and nausea/vomiting (4.9%).

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 nicardipine plasma levels. (7.3)
- Oral nicardipine increases cyclosporine plasma levels. Monitor cyclosporine levels when co-administering Cardene I.V. Premixed Injection (7.6)

**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)

Revised: 02/2009

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\*Sections or subsections omitted from the full prescribing information are not listed.

## 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 (2.6)*].

### 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 = 5 mL/hr
30 mg q8h	1.2 mg/hr = 12 mL/hr
40 mg q8h	2.2 mg/hr = 22 mL/hr

##### Dosage for Initiation of Therapy in a Patient not receiving oral nicardipine

Initiate therapy at 50 mL/hr (5.0 mg/hr). If desired blood pressure reduction is not achieved at this dose, the infusion rate may be increased by 25 mL/hr (2.5 mg/hr) every 5 minutes (for rapid titration) to 15 minutes (for gradual titration) up to a maximum of 150 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 30 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 (5.4, 5.5 and 5.6)*]

## **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 30-50 mL/hr (3.0 - 5.0 mg/hr) and adjusted to maintain desired blood pressure.

## **2.3 Instructions for Administration**

Administer Cardene IV 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 (5.7)*].

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**

1. Suspend container from eyelet support.
2. Remove protector from outlet port at bottom of container.
3. 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 20 mg (0.1 mg/mL) nifedipine 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 carefully 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 Adverse Reactions Observed in Clinical Trials

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	21 (15)	2 (2)
<b>Cardiovascular</b>		
Hypotension	8 (6)	1 (1)
Tachycardia	5 (4)	0
<b>Digestive</b>		
Nausea/vomiting	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 (5.4)*].

### **7.2 Cimetidine**

Cimetidine has been shown to increase nicardipine plasma concentrations with oral nicardipine administration. Patients receiving cimetidine and Cardene I.V. Premixed Injection concomitantly should be carefully monitored. 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, dipyridamole, 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 ( $\text{mg}/\text{m}^2$ ), but did occur in rabbits with oral doses at 24 times the maximum recommended human dose (MRHD) based on body surface area ( $\text{mg}/\text{m}^2$ ). 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 event include acidosis ( $\text{pH}<7.25$ ).

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 (marketed maternal weight gain suppression). New Zealand albino rabbits received oral nicardipine during organogenesis, at doses up to 16 times the MHRD 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 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.

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, use low initial doses in elderly patients, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

## 10. OVERDOSAGE

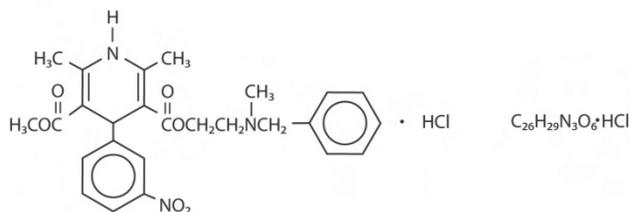
Several overdosages with orally administered nicardipine have been reported. One adult patient allegedly ingested 600 mg of immediate release oral nicardipine, and another patient, 2160 mg of the sustained release formulation of nicardipine. Symptoms included marked hypotension, bradycardia, palpitations, 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, implement standard measures including monitoring of cardiac and respiratory functions. Position the patient so as to avoid cerebral anoxia. Use vasopressors for patients exhibiting profound hypotension.

## 11. DESCRIPTION

Cardene (nicardipine hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium channel blocker). Cardene I.V. Premixed Injection for intravenous administration contains 20 mg of nicardipine hydrochloride per 200 mL (0.1 mg/mL) in either dextrose or sodium chloride. Nicardipine hydrochloride is a dihydropyridine derivative with IUPAC (International Union of Pure and Applied Chemistry) chemical name ( $\pm$ )-2-(benzyl-methyl amino) ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate monohydrochloride and has the following structure:



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 I.V. Premixed Injection is available as a ready-to-use sterile, non-pyrogenic, clear, colorless to yellow, iso-osmotic solution for intravenous administration in a 200 mL GALAXY container with 20 mg (0.1 mg/mL) nicardipine hydrochloride in either dextrose or sodium chloride.

### **Cardene I.V. Premixed Injection in 4.8% Dextrose**

20 mg in 200 mL (0.1 mg/mL)

Each mL contains 0.1 mg nicardipine hydrochloride, 48 mg dextrose hydrous, USP, 0.0192 mg citric acid, anhydrous, USP, and 1.92 mg sorbitol, NF. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH to 3.7 to 4.7.

### **Cardene I.V. Premixed Injection in 0.86% Sodium Chloride**

20 mg in 200 mL (0.1 mg/mL)

Each mL contains 0.1 mg nicardipine hydrochloride, 8.6 mg sodium chloride, USP, 0.0192 mg citric acid, anhydrous, USP, and 1.92 mg sorbitol, NF. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH to 3.7 to 4.7.

The GALAXY container is fabricated from multilayered plastic (PL 2501). Solutions are in contact with the polyethylene layer of the container and can leach out certain chemical components of the plastic in very small amounts within the expiration period. The suitability and safety of the plastic have been confirmed in tests in animals according to the USP biological tests for plastic containers, as well as by tissue culture toxicity studies.

## **12. CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

Nicardipine 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 produced relaxation of coronary vascular smooth muscle at drug levels which cause little or no negative inotropic effect.

### **12.2 Pharmacodynamics**

#### **Hemodynamics**

Cardene I.V. produces significant decreases in systemic vascular resistance. In a study of intra-arterially administered Cardene I.V., the degree of vasodilation and the resultant decrease in blood pressure were more prominent in hypertensive patients than in normotensive volunteers. Administration of Cardene I.V. to normotensive volunteers at dosages of 0.25 to 3.0 mg/hr for eight hours produced changes of <5 mmHg in systolic blood pressure and <3 mmHg in diastolic blood pressure.

An increase in heart rate is a normal response to vasodilation and decrease in blood pressure; in some patients these increases in heart rate may be pronounced. In placebo-controlled trials, the mean increases in heart rate were  $7 \pm 1$  bpm in postoperative patients and  $8 \pm 1$  bpm in patients with severe hypertension at the end of the maintenance period.

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). There is evidence that Cardene increases blood flow. Coronary dilatation induced by Cardene I.V. improves perfusion and aerobic metabolism in areas with chronic ischemia, resulting in reduced lactate production and augmented oxygen consumption. In patients with coronary artery disease, Cardene I.V., administered after beta-blockade, significantly improved systolic and diastolic left ventricular function.

In congestive heart failure patients with impaired left ventricular function, Cardene I.V. increased cardiac output both at rest and during exercise. Decreases in left ventricular end-diastolic pressure were also observed. However, in some patients with severe left ventricular dysfunction, it may have a negative inotropic effect and could lead to worsened failure.

“Coronary steal” has not been observed during treatment with Cardene I.V. (Coronary steal is the detrimental redistribution of coronary blood flow in patients with coronary artery disease from underperfused areas toward better perfused areas.) Cardene I.V. has been shown to improve systolic shortening in both normal and hypokinetic segments of myocardial muscle. Radionuclide angiography has confirmed that wall motion remained improved during increased oxygen demand. (Occasional patients have developed increased angina upon receiving oral nicardipine. Whether this represents coronary steal in these patients, or is the result of increased heart rate and decreased diastolic pressure, is not clear.)

In patients with coronary artery disease, Cardene I.V. improves left ventricular diastolic distensibility during the early filling phase, probably due to a faster rate of myocardial relaxation in previously underperfused 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. Cardene I.V. has no negative effect on myocardial relaxation at therapeutic doses. The clinical benefits of these properties have not yet been demonstrated.

### **Electrophysiologic Effects**

In general, no detrimental effects on the cardiac conduction system have been seen with Cardene I.V. During acute electrophysiologic studies, it increased heart rate and prolonged the corrected QT interval to a minor degree. It did not affect sinus node recovery or SA conduction times. The PA, AH, and HV intervals\* or the functional and effective refractory periods of the atrium were not prolonged. The relative and effective refractory periods of the His-Purkinje system were slightly shortened.

\*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.

### **Hepatic Function**

Because the liver extensively metabolizes nicardipine, plasma concentrations are influenced by changes in hepatic function. In a clinical study with oral nicardipine in patients with severe liver disease, plasma concentrations were elevated and the half-life was prolonged [*see Warnings and Precautions (5.5)*]. Similar results were obtained in patients with hepatic disease when Cardene I.V. (nicardipine hydrochloride) was administered for 24 hours at 0.6 mg/hr.

### **Renal Function**

When Cardene I.V. was given to mild to moderate hypertensive patients with moderate degrees of renal impairment, significant reduction in glomerular filtration rate (GFR) and effective renal

plasma flow (RPF) was observed. No significant differences in liver blood flow were observed in these patients. A significantly lower systemic clearance and higher area under the curve (AUC) were observed.

When oral nicardipine (20 mg or 30 mg TID) was given to hypertensive patients with impaired renal function, mean plasma concentrations, AUC, and  $C_{max}$  were approximately two-fold higher than in healthy controls. There is a transient increase in electrolyte excretion, including sodium [see *Warnings and Precautions* (5.6)].

Acute bolus administration of Cardene I.V. (2.5 mg) in healthy volunteers decreased mean arterial pressure and renal vascular resistance; glomerular filtration rate (GFR), renal plasma flow (RPF), and the filtration fraction were unchanged. In healthy patients undergoing abdominal surgery, Cardene I.V. (10 mg over 20 minutes) increased GFR with no change in RPF when compared with placebo. In hypertensive type II diabetic patients with nephropathy, oral nicardipine (20 mg TID) did not change RPF and GFR, but reduced renal vascular resistance.

### **Pulmonary Function**

In two well-controlled studies of patients with obstructive airway disease treated with oral nicardipine, no evidence of increased bronchospasm was seen. In one of the studies, oral nicardipine improved forced expiratory volume 1 second (FEV<sub>1</sub>) and forced vital capacity (FVC) in comparison with metoprolol. Adverse experiences reported in a limited number of patients with asthma, reactive airway disease, or obstructive airway disease are similar to all patients treated with oral nicardipine.

## **12.3 Pharmacokinetics**

### **Distribution**

Rapid dose-related increases in nicardipine plasma concentrations are seen during the first two hours after the start of an infusion of Cardene I.V. Plasma concentrations increase at a much slower rate after the first few hours, and approach steady state at 24 to 48 hours. The steady-state pharmacokinetics of nicardipine are similar in elderly hypertensive patients (>65 years) and young healthy adults). On termination of the infusion, nicardipine concentrations decrease rapidly, with at least a 50% decrease during the first two hours post-infusion. The effects of nicardipine on blood pressure significantly correlate with plasma concentrations. Nicardipine is highly protein bound (>95%) in human plasma over a wide concentration range.

Following infusion, nicardipine plasma concentrations decline tri-exponentially, with a rapid early distribution phase ( $\alpha$ -half-life of 2.7 minutes), an intermediate phase ( $\beta$ -half-life of 44.8 minutes), and a slow terminal phase ( $\gamma$ -half-life of 14.4 hours) that can only be detected after long-term infusions. Total plasma clearance (Cl) is 0.4 L/hr•kg, and the apparent volume of distribution ( $V_d$ ) using a non-compartment model is 8.3 L/kg. The pharmacokinetics of Cardene I.V. are linear over the dosage range of 0.5 to 40.0 mg/hr.

### **Metabolism and Excretion**

Cardene I.V. has been shown to be rapidly and extensively metabolized by the liver. Nicardipine does not induce or inhibit its own metabolism and does not induce or inhibit hepatic microsomal enzymes.

After coadministration of a radioactive intravenous dose of Cardene I.V. with an oral 30 mg dose given every 8 hours, 49% of the radioactivity was recovered in the urine and 43% in the feces within 96 hours. None of the dose was recovered as unchanged nicardipine.

## **13. NONCLINICAL TOXICOLOGY**

### **13.1 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 (human equivalent dose about 16 mg/kg/day, 8 times the maximum recommended oral dose).

### **13.3 Reproductive and Developmental Toxicology**

Embryotoxicity, but no teratogenicity, was seen at intravenous doses of 10 mg nicardipine/kg/day in rats and 1 mg/kg/day in rabbits. These doses in the rat and rabbit are equivalent to human IV doses of about 1.6 mg/kg/day and 0.32 mg/kg/day respectively. (The total daily human dose delivered by a continuous IV infusion ranges from 1.2 to 6 mg/kg/day, depending on duration at different infusion rates ranging from 3 to 15 mg/hr as individual patients are titrated for optimal results.) Nicardipine was also embryotoxic 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 (human equivalent dose about 16 mg/kg/day or about 8 times the maximum recommended human oral dose). No adverse effects on the fetus were observed when New Zealand albino rabbits were treated orally, 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 doses of up to 100 mg/kg/day (human equivalent dose about 16 mg/kg/day) there was no evidence of embryotoxicity or teratogenicity. However, dystocia, reduced birth weight, reduced neonatal survival and reduced neonatal weight gain were noted.

## 14. CLINICAL STUDIES

### Effects In Hypertension

In patients with mild to moderate chronic stable essential hypertension, Cardene I.V. (0.5 to 4.0 mg/hr) produced dose-dependent decreases in blood pressure. At the end of a 48-hour infusion at 4.0 mg/hr, the decreases were 26.0 mmHg (17%) in systolic blood pressure and 20.7 mmHg (20%) in diastolic blood pressure. In other settings (e.g., patients with severe or postoperative hypertension), Cardene I.V. (5 to 15 mg/hr) produced dose-dependent decreases in blood pressure. Higher infusion rates produced therapeutic responses more rapidly. The mean time to therapeutic response for severe hypertension, defined as diastolic blood pressure  $\leq 95$  mmHg or  $\geq 25$  mmHg decrease and systolic blood pressure  $\leq 160$  mmHg, was  $77 \pm 5.2$  minutes. The average maintenance dose was 8.0 mg/hr. The mean time to therapeutic response for postoperative hypertension, defined as  $\geq 15\%$  reduction in diastolic or systolic blood pressure, was  $11.5 \pm 0.8$  minutes. The average maintenance dose was 3.0 mg/hr.

## 16. HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

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 20 mg (0.1 mg/mL) nifedipine hydrochloride in either dextrose or sodium chloride.

Pack Size	Diluent	NDC Number
10 bags, each containing 20 mg in 200 mL (0.1mg/mL)	4.8% Dextrose	NDC 24477-312-02
10 bags, each containing 20 mg in 200 mL (0.1mg/mL)	0.86% Sodium Chloride	NDC 24477-311-02

### 16.2 Storage and Handling

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.

Manufactured by:  
Baxter Healthcare Corporation  
Deerfield, IL 60015 USA

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

To report an adverse event, record the lot number and call Drug Safety at 1-877-207-5802.

Revised February 2009

CAR09-210

07-19-59-674

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**019734Orig1s013**

**CHEMISTRY REVIEW(S)**

**Division of Post Approval Marketing Evaluation IV  
Chemist Review of Supplement**

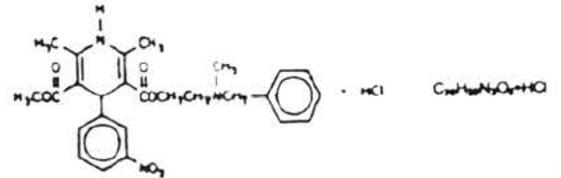
- 1. Organization HFD-110
- 2. NDA Number: 19734
- 3. Supplement Numbers/Dates: SCM-013/SCF-013 BC  
Letter Date: March 31, 2008; June 12, 2008  
Stamp Date: April 2, 2008; June 13, 2008
- 4. Amendments/Reports/Dates:
- 5. Received by Chemist: July 9, 2008/June 18, 2008

6. Applicant Name and Address: PDL Biopharma, Inc.  
1400 Seaport Blvd.  
Redwood City, CA 98063

7. Name of the Drug: Cardene® I.V.  
8. Nonproprietary name: nicardipine hydrchloride

9. Chemical Structure/ Chemical Name:

10. Dosage Forms: Premixed injection in Dextrose or Saline



- 11. Potency: 0.1mg/ml
- 12. Pharmacological Category: hypertension
- 13. How Dispensed: XXX (RX) \_\_\_\_\_ (OTC)
- 14. Records and Reports current XXX (yes) \_\_\_\_\_ (No)
- 15. Related IND/NDA/DMF: \_\_\_\_\_ (yes) XXX (No)

16. **Comments:** This PA supplement provides for a new container closure system for Cardene I.V. Currently Cardene IV is available in ampules at a concentration of 2.5mg/ml. Prior to administration, the ampule drug product must be diluted with an intravenous fluid to a final concentration of 0.1mg/ml. The proposed new container system is GALAXY® intravenous bags which contain 0.1mg/ml of Cardene I.V. in a premixed dextrose or saline formulation in a ready to use presentation. The GALAXY bag manufacture, quality control and (b)(4) is referenced to DMF (b)(4) and an LOA is provided.

18. **Conclusions:** Sufficient data is provided to support the use of the GALAXY bags as a container for the premixed IV solution of nicardipine hydrochloride in dextrose or saline. Unidentified peaks are noted, as related substance, and are maintained at less than approved specification limits of NMT (b)(4). The release and stability specifications are the same as those approved for the ampules. An extractable/ leachables study with the drug product in the GALAXY bags, has indicated low levels (ppb range) of some potential leachables. (b)(4)

Furthermore, toxicology tests have shown no adverse effects in a 30 day, repeat dose study. Stability data also supports the new premixed bags when stored at room temperature through 6 months. Based on the current stability data, a 12 month

*expiry is reasonable. Labeling, adequately addresses the proposed changes, and deletes any reference to the ampules.*

**19. Recommendations:** Recommend Approval of the PA Supplement.

Reviewer Name

\_\_\_\_\_  
Julia C. Pinto, Ph.D., Chemist

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Julia Pinto  
7/24/2008 04:39:06 PM  
CHEMIST

Jim Vidra  
7/24/2008 04:51:26 PM  
CHEMIST

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**019734Orig1s013**

**MICROBIOLOGY/VIROLOGY REVIEW(S)**

# Product Quality Microbiology Review

21 July 2008

**NDA:** 19-734/SCF-013

**Drug Product Name**

**Proprietary:** Cardene I.V® in 5% Dextrose & 0.9% Sodium Chloride

**Non-proprietary:** nicardipine hydrochloride 0.1 mg/mL

**Drug Product Priority Classification:** S1

**Review Number:** 1

**Dates of Submission(s) Covered by this Review**

Letter	Stamp	Review Request	Assigned to Reviewer
March 13, 2008	March 14, 2008	June 12, 2008	June-23-2008

**Submission History (for amendments only) – N/A**

**Applicant/Sponsor**

**Name:** PDL BioPharma, Inc.

**Address:** 1400 Seaport Blvd., Redwood City, CA 94063

**Representative:** Jill A. Henrich, Executive Director, Reg. Affairs

**Telephone:** [REDACTED] (b) (6) or Nancy Teasdale [REDACTED] (b) (6)

**Name of Reviewer:** Vinayak. B. Pawar, Ph.D.

**Conclusion:** The application is recommended for approval from microbiology product quality standpoint.

---

## Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUBMISSION:** Prior Approval Supplement
2. **SUBMISSION PROVIDES FOR:** Addition of a new container closure system for Cardene I.V. drug product.
3. **MANUFACTURING SITE:** Baxter Health Care Round Lake, IL
4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Intramuscular injection, 0.1 mg/mL premixed in 5% Dextrose or 0.9% Sodium Chloride.
5. **METHOD(S) OF STERILIZATION:** (b) (4)
6. **PHARMACOLOGICAL CATEGORY:** Treatment of Hypertension.
- B. **SUPPORTING/RELATED DOCUMENTS:** DMF (b) (4)
- C. **REMARKS:** The consult request review of a Prior Approval Supplement NDA 19-734/SCF013 for addition of a new GALAXY (b) (4) container in place of the currently approved ampoule. A single volume of the application was provided as a hard copy. The drug product will be (b) (4) in the new container at Baxter Health Care facility.

**filename:** C:\my documents\reviews\supplements\NO19734S013R1

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## **Executive Summary**

### **I. Recommendations**

- A. Recommendation on Approvability** – The application is recommended for approval from microbiology product quality standpoint based on the satisfactory review of DMF (b)(4)
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

### **II. Summary of Microbiology Assessments**

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – There are no changes in the manufacturing process except for the change in container closure system.
- B. Brief Description of Microbiology Deficiencies** - None
- C. Assessment of Risk Due to Microbiology Deficiencies** – N/A

### **III. Administrative**

- A. Reviewer's Signature** \_\_\_\_\_  
Vinayak. B. Pawar, Ph.D.
- B. Endorsement Block** \_\_\_\_\_  
Bryan S. Riley, Ph.D.
- C. CC Block**  
N/A

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this page is the manifestation of the electronic signature.**  
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/s/

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Vinayak Pawar  
7/23/2008 12:27:02 PM  
MICROBIOLOGIST

Recommended for approval from microbiology product quality standpoint.

Bryan Riley  
7/23/2008 01:06:12 PM  
MICROBIOLOGIST  
I concur.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**019734Orig1s013**

**OTHER REVIEW(S)**

**RHPM Review of Draft Label  
NDA 19-734/013**

**Date of Original Submission:** March 31, 2008  
**Date of AE Letter:** N/A  
**Draft Labeling Approved:** July 31, 2008  
**Date of Review:** July 30, 2008  
**Sponsor Name:** EKR Therapeutics, Inc.  
**Product(s) Name:** Cardene (nicardipine hydrochloride) 2.5 mg/mL Intravenous Solution  
Cardene IV 0.1 mg/mL Pre-mixed Injection in 5% Dextrose  
Cardene IV 0.1 mg/mL Pre-mixed Injection in 0.9% Sodium Chloride

**Evaluation:**

This prior approval supplement is proposed to support the addition of a new container closure system for Cardene IV drug product. The current Cardene IV drug product is available in an amber ampul at a concentration of 2.5 mg/mL nicardipine hydrochloride. Prior to administration, the ampul drug product must be diluted with an intravenous fluid to a final concentration of 0.1 mg/mL. The proposed new container closure system is a GALAXY® intravenous (IV) bag which contains a concentration of 0.1 mg/mL nicardipine hydrochloride. This application supports two 0.1 mg/mL nicardipine hydrochloride premixed ready-to-use presentations of the currently marketed Cardene IV ampul after dilution. The nicardipine hydrochloride is diluted with either 5% Dextrose or 0.9% Sodium Chloride.

**The following changes have been proposed by the sponsor:**

1. Immediately following the product name, CARDENE I.V. (nicardipine hydrochloride), the following text has been added:  
  
“Premixed injection in either 4.8% Dextrose or 0.86% Sodium Chloride”
2. Under the **DESCRIPTION** section, the following sentence has been changed  
**From:**  
Cardene® I.V. for intravenous administration contains 2.5 mg/mL of nicardipine hydrochloride.  
  
**To:**  
Cardene I.V. premixed injection for intravenous administration contains 20 mg of nicardipine hydrochloride per 200 mL (0.1 mg/mL) in either dextrose or sodium chloride.
3. Under the **DESCRIPTION** section, the following text has been changed  
**From:**  
Cardene® I.V. is available as a sterile, non-pyrogenic, clear, yellow solution in 10 mL ampuls for intravenous infusion after dilution. Each mL contains 2.5 mg

nicardipine hydrochloride in Water for Injection, USP with 48.00 mg Sorbitol, NF, buffered to pH 3.5 with 0.525 mg citric acid monohydrate, USP and 0.09 mg sodium hydroxide, NF. Additional citric acid and/or sodium hydroxide may have been added to adjust pH.

**To:**

Cardene I.V. premixed injection is available as a ready-to-use sterile, non-pyrogenic, clear, colorless to yellow, iso-osmotic solution for intravenous administration in a 200 mL GALAXY<sup>®</sup> container with 20 mg (0.1 mg/mL) nicardipine hydrochloride in either dextrose or sodium chloride.

**Cardene I.V. Premixed Injection in 4.8% Dextrose**

20 mg in 200 mL (0.1 mg/mL)

Each mL contains 0.1 mg nicardipine hydrochloride, 48 mg dextrose hydrous, USP, 0.0192 mg citric acid, anhydrous, USP, and 1.92 mg sorbitol, NF.

Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH to 3.7 to 4.7.

**Cardene I.V. Premixed Injection in 0.86% Sodium Chloride**

20 mg in 200 mL (0.1 mg/mL)

Each mL contains 0.1 mg nicardipine hydrochloride, 8.6 mg sodium chloride, USP, 0.0192 mg citric acid, anhydrous, USP, and 1.92 mg sorbitol, NF.

Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH to 3.7 to 4.7.

The GALAXY plastic container is fabricated from a specially designed multilayered plastic (PL 2501). Solutions are in contact with the polyethylene layer of the container and can leach out certain chemical components of the plastic in very small amounts within the expiration period. The suitability and safety of the plastic have been confirmed in tests in animals according to the USP biological tests for plastic containers, as well as by tissue culture toxicity studies.

4. Under the **DOSAGE AND ADMINISTRATION** section, “premixed injection” has been added to the first sentence.
5. Under the **DOSAGE AND ADMINISTRATION, PREPARATION** subsection, the following language has been changed

**From:**

**WARNING: AMPULS MUST BE DILUTED BEFORE INFUSION**

*Dilution:* Cardene<sup>®</sup> I.V. is administered by slow continuous infusion at a CONCENTRATION OF 0.1 MG/ML. Each ampul (25 mg) should be diluted with 240 mL of compatible intravenous fluid (see below), resulting in 250 mL of solution at a concentration of 0.1 mg/mL.

Cardene<sup>®</sup> I.V. has been found to be compatible and stable in glass or polyvinyl chloride containers for 24 hours at controlled room temperature with:

Dextrose (5%) Injection, USP

Dextrose (5%) and Sodium Chloride (0.45%) Injection, USP

Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP

Dextrose (5%) with 40 mEq Potassium, USP

Sodium Chloride (0.45%) Injection, USP

Sodium Chloride (0.9%) Injection, USP

***Cardene<sup>®</sup> I.V. is NOT compatible with Sodium Bicarbonate (5%) Injection, USP or Lactated Ringer's Injection, USP.***

THE DILUTED SOLUTION IS STABLE FOR 24 HOURS AT ROOM TEMPERATURE.

*Inspection:* As with all parenteral drugs, Cardene<sup>®</sup> I.V. should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Cardene<sup>®</sup> I.V. is normally light yellow in color.

**To:**

**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:**

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

6. Under the **HOW SUPPLIED** section, the following text has been changed

**From:**

Cardene<sup>®</sup> I.V. (nicardipine hydrochloride) is available in packages of 10 ampuls of 10 mL as follows:

25 mg (2.5 mg/mL), NDC 67286-0812-3.

**Store at controlled room temperature 20° to 25°C (68° to 77°F), refer to USP Controlled Room Temperature.**

**Freezing does not adversely affect the product, but exposure to elevated temperatures should be avoided.**

**Protect from light. Store ampuls in carton until used.**

U S Patent No.: 5,164,405

Cardene<sup>®</sup> I.V. is a registered trademark of PDL BioPharma Inc.

Manufactured by:  
Baxter Healthcare Corporation  
Deerfield, IL 60015 USA

Marketed by:  
PDL BioPharma, Inc.  
Fremont, CA 94555

For questions of a medical nature call 1-866-437-7742

Revised October 2007

© Copyright 2007 PDL BioPharma, Inc. Fremont, CA 94555

462-443-00                      120104

**To:**

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 20 mg (0.1 mg/mL) nicardipine hydrochloride in either dextrose or sodium chloride.

**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.

PDL BioPharma, Inc. patent pending.

Cardene<sup>®</sup> I.V. is a registered trademark of PDL BioPharma Inc.

Baxter and GALAXY are registered trademarks of Baxter International Inc.

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

Marketed by:  
PDL BioPharma, Inc.  
Redwood City, CA 94063

To report an adverse event, record the lot number and call Drug Safety at 1-866-437-7742

Revised March 2008

© Copyright 2007 PDL BioPharma, Inc. Redwood City, CA 94063 USA  
07-19-55-613 161301

**Minor Editorial Revision:**

I also note the registered trademark symbol, ®, has been deleted throughout the entire package insert.

**Recommendation:**

Based on the approval recommendations from the chemist, Dr. Julia Pinto and microbiologist, Dr. Vinayak Pawar, an approval letter should issue for this supplement with the changes proposed by the sponsor.

Alisea Crowley, Pharm.D.

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Alisea R. Crowley  
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CSO

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**019734Orig1s013**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## REQUEST FOR CONSULTATION

TO (Office/Division): Jim McVey, HFD-805, 301-796-1572

FROM (Name, Office/Division, and Phone Number of Requestor): Teshara G. Bouie, ONDQA, Division of Post-Marketing Assessment, 301-796-1649

DATE  
June 12, 2008

IND NO.

NDA NO.  
19-734

TYPE OF DOCUMENT  
SCF-013

DATE OF DOCUMENT  
March 13, 2008

NAME OF DRUG  
Cardene

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
July 15, 2008

NAME OF FIRM: EKR Therap

### REASON FOR REQUEST

#### I. GENERAL

- |   |  |  |
|---|--|--|
| <input type="checkbox"/> NEW PROTOCOL                               | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT                            | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE                         | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING                           | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT                    | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input checked="" type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY                         | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |   |  |
|---|--|
| <input type="checkbox"/> DISSOLUTION            | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILTY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** This supplement provides for the addition of a new container closure system for Cardene I.V. drug product. Please review.

PDUFA Goal date: August 2, 2008

SIGNATURE OF REQUESTOR  
Teshara G. Bouie

METHOD OF DELIVERY (Check one)  
 DFS     EMAIL     MAIL     HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Teshara Bouie

6/12/2008 04:47:41 PM