Trade Name: CARDENE I.V.

Generic or Proper Name: nicardipine hydrochloride

Sponsor: Chiesi USA Inc.

Approval Date: November 7, 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.
## CONTENTS

Reviews / Information Included in this NDA Review.

<table>
<thead>
<tr>
<th>Reviews / Information Included in this NDA Review</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval Letter</td>
<td>X</td>
</tr>
<tr>
<td>Other Action Letters</td>
<td></td>
</tr>
<tr>
<td>Labeling</td>
<td>X</td>
</tr>
<tr>
<td>REMS</td>
<td></td>
</tr>
<tr>
<td>Summary Review</td>
<td></td>
</tr>
<tr>
<td>Officer/Employee List</td>
<td></td>
</tr>
<tr>
<td>Office Director Memo</td>
<td></td>
</tr>
<tr>
<td>Cross Discipline Team Leader Review</td>
<td></td>
</tr>
<tr>
<td>Medical Review(s)</td>
<td></td>
</tr>
<tr>
<td>Chemistry Review(s)</td>
<td>X</td>
</tr>
<tr>
<td>Environmental Assessment</td>
<td></td>
</tr>
<tr>
<td>Pharmacology Review(s)</td>
<td></td>
</tr>
<tr>
<td>Statistical Review(s)</td>
<td></td>
</tr>
<tr>
<td>Microbiology / Virology Review(s)</td>
<td>X</td>
</tr>
<tr>
<td>Clinical Pharmacology/Biopharmaceutics Review(s)</td>
<td>X</td>
</tr>
<tr>
<td>Other Reviews</td>
<td>X</td>
</tr>
<tr>
<td>Risk Assessment and Risk Mitigation Review(s)</td>
<td></td>
</tr>
<tr>
<td>Proprietary Name Review(s)</td>
<td></td>
</tr>
<tr>
<td>Administrative/Correspondence Document(s)</td>
<td>X</td>
</tr>
</tbody>
</table>
NDA 19-734/S-014

EKR Therapeutics, Inc.
Attention: Alexander Mironov
Director, Regulatory Affairs
1545 US Highway 206, 3rd Floor
Bedminster, NJ 07921

Dear Mr. Mironov:

Please refer to your supplemental new drug application dated May 14, 2008, received May 15, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cardene (nicardipine hydrochloride) 0.2 mg/mL Premixed Injection in 5% Dextrose, and Cardene (nicardipine hydrochloride) 0.2 mg/mL Premixed Injection in 0.83% Sodium Chloride.

We acknowledge receipt of your submissions dated August 12, 2008 and November 3, 2008. This supplemental new drug application provides for the addition of a new container closure system for the Cardene I.V. drug product and an increase in the concentration of the nicardipine hydrochloride to 0.2 mg/mL.

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 draft labeling submitted on May 14, 2008 and the immediate carton and container labeling submitted on November 3, 2008.

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(1)] in structured product labeling (SPL) format described at http://www.fda.gov/oc/datacouncil/sp.html that is identical to the enclosed labeling text (text for the package insert) submitted May 14, 2008. 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 19734/S-014.”

Please submit final printed carton and container labels that are identical to the November 3, 2008 carton and immediate container labels 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 Application 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-014.” Approval of this submission by FDA is not required before the labeling is used.
Marketing the products with labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

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:

Lori Wachter RN, BSN
Regulatory Project Manager
(301) 796 3975.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Package insert and carton and container labeling
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

---------------------
Norman Stockbridge
11/7/2008 02:47:19 PM
Cardene I.V.
(nicardipine hydrochloride)

Premixed Injection in either 4.8% Dextrose or 0.86% Sodium Chloride

Rx only

**Description**
Cardene (nicardipine HCl) is a calcium ionophore blocker (dye channel blocker or calcium channel blocker). Cardene I.V. premixed injection for intravenous administration contains 20 mg of nicardipine hydrochloride per 200 mL of solution in either 4.8% dextrose or 0.86% sodium chloride. Nicardipine hydrochloride is a dihydropyridine derivative with UPRC (International Union of Pure and Applied Chemistry) chemical name (2R,5S)-1-benzyl-2-ethyl-3-phenylethanol (1+4)-dimethyl-3,5,8-trimethylcyclohexane benzyl alcohol and has the following structure:

![Nicardipine Structure](image)

Nicardipine hydrochloride is a granular-yellow, sublimate, crystalline powder that melts at about 178°C. It is freely soluble in chloroform, methanol, and glacial acetic acid, sparingly soluble in anhydrous ethanol, slightly soluble in water, and insoluble in ethyl alcohol and propylene glycol in benzene. It has a molecular weight of 515.6.

Cardene I.V. premixed injection is available as a ready-to-use vial, non-pyrogenic, colorless to yellow, translucent to clear, colorless to yellow, sodium chloride injection premixed with 20 mg/200 mL (0.1% w/v) nicardipine hydrochloride in either dextrose or sodium chloride.

**Cardene I.V. Therapeutic Use in 4.8% Dextrose**
20 mL in 200 mL (0.1 mL/g)
Each mL contains 0.1 mg nicardipine hydrochloride, 48 mL dextrose base, USP; 0.19% citric acid, USP; and 0.06% sodium chloride, USP.

**Cardene I.V. Therapeutic Use in 0.86% Sodium Chloride**
20 mL in 200 mL (0.1 mL/g)
Each mL contains 0.1 mg nicardipine hydrochloride, 3 mg sodium chloride, USP; 0.05% citric acid, sodium chloride, USP; and 1.0 mL water. MF: Hydrochloric acid and sodium chloride hydrochloride may have been added to adjust pH to 7.3 to 7.4.

**Cardene I.V. Premixed Injection in 0.86% Sodium Chloride**
20 mL in 200 mL (0.1 mL/g)
Each mL contains 0.1 mg nicardipine hydrochloride, 3 mg sodium chloride, USP; 0.05% citric acid, sodium chloride, USP; and 1.0 mL water. MF: Hydrochloric acid and sodium chloride hydrochloride may have been added to adjust pH to 7.3 to 7.4.

**Cardene I.V. Injection**
All Cardene I.V. injection solutions are fabricated from a specially designed modified plastic (PDLM). 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.

**Clinical Pharmacology**

**MECHANISM OF ACTION**
Cardene inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle without changing cell membrane potentials. 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 effectiveness of calcium blockers is more selective for vascular smooth muscle than cardiac muscle. In general, Cardene produced relaxation of coronary vascular smooth muscle at drug concentrations which cause little or no negative inotropic effect.

**PHARMACODYNAMICS AND METABOLISM**
Following intravenous administration, the peak plasma concentration is observed at approximately 2 hours (range 1-4 to 2 hours). An elimination phase (t1/2 of 4 hours) and a slower terminal phase (t1/2 of 7 hours) are not observed. Total plasma clearance (CL) is 0.14 mL/min, and the apparent volume of distribution (Vd) is approximately 0.1 L/kg. The pharmacokinetics of Cardene I.V. is dependent on the dose range of 1 to 8 mg/kg.

**Pharmacokinetic properties**
- **Rapid onset:** Cardene is rapidly distributed into cardiac and vascular tissues. Plasma concentrations are seen one hour after the first 20-minute infusion. The elimination phase follows the first 20-minute period and is characterized by a single phase with a terminal half-life of 5 hours. The elimination half-life is 5 hours.
- **Cardene is highly protein-bound (98%) in human plasma per a weight concentration ratio.**
- **Cardene has been shown to be rapid and extensively reabsorbed from the liver.** After intravenous administration of a single dose of Cardene I.V. using a 10 ml dose, 80% of the radioactive

- **Cardene is highly protein-bound (98%) in human plasma per a weight concentration ratio.**

- **Cardene has been shown to be rapid and extensively reabsorbed from the liver.** After intravenous administration of a single dose of Cardene I.V. using a 10 ml dose, 80% of the radioactive

**Adverse Reactions**
Adverse reactions to Cardene I.V. have been reported in patients receiving the oral formulation of the drug. Adverse reactions reported in patients receiving the oral formulation were:

- **Cardene I.V. is contraindicated in patients with known hypersensitivity to the drug.** Cardene I.V. is also contraindicated in patients with advanced aortic sclerosis because of the drug's tendency to cause hypotension.

**Indications and Usage**
Cardene I.V. is indicated for the short-term treatment of hypertension when oral therapy is not feasible or not acceptable.

**For prolonged control of blood pressure, patients should be transferred to oral medication as soon as their clinical condition permits (see “Dosage and Administration”)**

**Contraindications**
Cardene I.V. is contraindicated in patients with known hypersensitivity to the drug. Cardene I.V. is also contraindicated in patients with advanced aortic sclerosis because of the drug's tendency to cause hypotension.

**Warnings**

**Beta-blocker Withdrawal**
Nicardipine is a non-beta-blocker and therefore requires no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be gradually reduced to dose of beta-blocker.

**Rapid Decrease in Blood Pressure**
No clinical events have been reported suggesting a too rapid decrease in blood pressure with Cardene I.V. However, as with any antihypertensive agent, blood pressure lowering should be accompanied as long as it is compatible with the patient's clinical status.

**Use in Patients with Atherosclerosis**
Increased in frequency, duration, or severity of angina have been seen in chronic oral therapy with Cardene capsules. Cardene is an oral antianginal agent and may be used safely in patients who are on other antianginal agents, including nitrates.

**Cardene I.V. Contraindicated in Patients with Known Hypersensitivity to the Drug**
Cardene I.V. is contraindicated in patients with known hypersensitivity to the drug. Cardene I.V. is also contraindicated in patients with advanced aortic sclerosis because of the drug's tendency to cause hypotension.

**Peripheral Vascular Insufficiency**
Only limited clinical experience exists in use of Cardene I.V. for patients with hypertension associated with peripheral vascular disease. Cardene I.V. should therefore be exercised when using the drug in these patients.

**Precautions**

**General**

**Blood Pressure:** Because Cardene I.V. decreases peripheral resistance, monitoring of blood pressure during..."
IN VITRO (see "Warning")

Cardene capsule is usually administered orally. Cardene IV is administered by slow intravenous infusion at a concentration 0.1 mg/mL with constant infusion pressure to fall within 45 minutes. It reaches about 50% of its ultimate decrease in about 45 minutes and does not reach steady state until about 10 hours. Blood pressure, pulse, and temperature should be closely monitored during and after the administration of Cardene IV. Cardene IV should be used with caution in patients with documented or suspected heart block.

Dosing and Administration Cardene IV, simulated by hydrophilic sustained-release, is administered for intravenous use. It is also intended for intermittent use. In general, the following schedule is intended to maintain the therapeutic response over a period of several hours. Cardene IV is administered in a concentration 0.1 mg/mL with constant infusion pressure to fall within 45 minutes. It reaches about 50% of its ultimate decrease in about 45 minutes and does not reach steady state until about 10 hours. Blood pressure, pulse, and temperature should be closely monitored during and after the administration of Cardene IV. Cardene IV should be used with caution in patients with documented or suspected heart block.

Dosage and Administration Cardene IV, simulated by hydrophilic sustained-release, is administered for intravenous use. It is also intended for intermittent use. In general, the following schedule is intended to maintain the therapeutic response over a period of several hours. Cardene IV is administered in a concentration 0.1 mg/mL with constant infusion pressure to fall within 45 minutes. It reaches about 50% of its ultimate decrease in about 45 minutes and does not reach steady state until about 10 hours. Blood pressure, pulse, and temperature should be closely monitored during and after the administration of Cardene IV. Cardene IV should be used with caution in patients with documented or suspected heart block.

Dosage and Administration Cardene IV, simulated by hydrophilic sustained-release, is administered for intravenous use. It is also intended for intermittent use. In general, the following schedule is intended to maintain the therapeutic response over a period of several hours. Cardene IV is administered in a concentration 0.1 mg/mL with constant infusion pressure to fall within 45 minutes. It reaches about 50% of its ultimate decrease in about 45 minutes and does not reach steady state until about 10 hours. Blood pressure, pulse, and temperature should be closely monitored during and after the administration of Cardene IV. Cardene IV should be used with caution in patients with documented or suspected heart block.

Dosage and Administration Cardene IV, simulated by hydrophilic sustained-release, is administered for intravenous use. It is also intended for intermittent use. In general, the following schedule is intended to maintain the therapeutic response over a period of several hours. Cardene IV is administered in a concentration 0.1 mg/mL with constant infusion pressure to fall within 45 minutes. It reaches about 50% of its ultimate decrease in about 45 minutes and does not reach steady state until about 10 hours. Blood pressure, pulse, and temperature should be closely monitored during and after the administration of Cardene IV. Cardene IV should be used with caution in patients with documented or suspected heart block.
APPLICATION NUMBER:

019734Orig1s014

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-014/SCF-014 BC
   Letter Date: May 14 2008; August 12 2008
   Stamp Date: May 15, 2008; August 13, 2008
4. Amendments/Reports/Dates:
5. Received by Chemist: June 27/August 28, 2008

6. Applicant Name and Address: EKR Therapeutics
   1545 US Highway Route 206
   Bedminster, NJ 07921

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

9. Chemical Structure/Chemical Name:
10. Dosage Forms: Premixed injection in Dextrose or Saline
11. Potency: 0.2mg/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 will contain in increase in concentration to 0.2mg/ml of Cardene I.V. in a premixed dextrose or saline formulation in a ready to use presentation. The container closure system for the 0.1mg/ml concentration has been approved under S-013. The results of a BE study is provided in support of the new concentration. The GALAXY bag manufacture, quality control and is referenced to DMF and an LOA is provided.

18. Conclusions: Evaluation: Adequate. 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 at a concentration of 0.2mg/ml. Unidentified peaks are noted, as related substance, and are maintained at below the approved specification limits of NMT. The release and stability specifications are the same as those approved for the ampules and for the 0.1mg/ml premixed bag. An extractable/leachables study with the drug product in the GALAXY bags, has indicated low levels (ppb range) of some potential leachables.
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.


Reviewer Name

Julia C. Pinto, Ph.D., Chemist

12 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
---------------------
Julia Pinto
9/4/2008 07:07:36 PM
CHEMIST

Jim Vidra
9/5/2008 08:56:35 AM
CHEMIST
APPLICATION NUMBER:

019734Orig1s014

MICROBIOLOGY/VIROLOGY REVIEW(S)
Product Quality Microbiology Review

12 August 2008

NDA: 19-734/SCF-014

Drug Product Name
Proprietary: Cardene I.V® 0.2 mg/mL in 5% Dextrose & 0.9% Sodium Chloride
Non-proprietary: nicardipine hydrochloride 0.2 mg/mL
Drug Product Priority Classification: S1

Review Number: 1

Dates of Submission(s) Covered by this Review

<table>
<thead>
<tr>
<th>Letter Stamp</th>
<th>Review Request</th>
<th>Assigned to Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>May 15, 2008</td>
<td>March 18, 2008</td>
<td>June 12, 2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>June 23, 2008</td>
</tr>
</tbody>
</table>

Submission History (for amendments only) – N/A

Applicant/Sponsor
Name: EKR Therapeutics, Inc.
Address: 545 US Highway Rt 206, Bedminster, NJ 07921
Representative: Alexander Mironov, Director, Regulatory Affairs
Telephone: 877-435-2524 ext. 123, or Nancy Teasdale

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 and an increase in drug concentration from 0.1 mg/mL to 0.2 mg/mL.

3. MANUFACTURING SITE:  Baxter Health Care Round Lake, IL

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:  Intramuscular injection, 0.2 mg/mL premixed in 5% Dextrose or 0.9% Sodium Chloride.

5. METHOD(S) OF STERILIZATION:

6. PHARMACOLOGICAL CATEGORY:  Treatment of Hypertension.

B. SUPPORTING/RELATED DOCUMENTS:  DMF

C. REMARKS:  The consult request review of a Prior Approval Supplement NDA 19-734/SCF014 for addition of a new GALAXY container in place of the currently approved ampoule and to increase the concentration of the drug from 0.1 mg/mL to 0.2 mg/mL. This new container will help provide the drug in a ready-to-use format rather than the previous presentation where the drug was diluted in 5% Dextrose or 0.9% Sodium Chloride before administration. EKR assumed regulatory responsibility for Cardene I.V. from PDL BioPharma, Inc. on May 6, 2008. Hard copies of Module 1 (1 volume), Module 5 (1 volume), and Module 3 (5 volumes) were provided for review. The drug product will be in the new container at Baxter Health Care facility.

filename: C:\my documents\reviews\supplements\NO19734S014R1
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. 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 and an increased concentration of the drug from 0.1 mg/mL to 0.2 mg/mL.

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

/s/
---------------------
Vinayak Pawar
8/12/2008 02:31:13 PM
MICROBIOLOGIST

Recommended for approval.

James McVey
8/12/2008 02:35:09 PM
MICROBIOLOGIST
I concur.
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019734Orig1s014

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)
<table>
<thead>
<tr>
<th><strong>NDA</strong></th>
<th>19-734</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NDA type</strong></td>
<td>Supplement SCF-014: Prior Approval Supplement/Formulation Change Supplement</td>
</tr>
<tr>
<td><strong>Submission Date</strong></td>
<td>May 14, 2008</td>
</tr>
</tbody>
</table>
| **Brand Name** | Cardene® IV (nicardipine HCl) 0.2 mg/ml Pre-mixed Injection in 5% Dextrose  
Cardene IV® (nicardipine HCl) 0.2 mg/ml Pre-mixed Injection in 0.83% Sodium Chloride |
| **Generic Name** | Nicardipine Hydrochloride |
| **Reviewer** | Angelica Dorantes, PhD |
| **Team Leader (Acting)** | Robert Kumi, PhD |
| **OCP Division** | Clinical Pharmacology 1 (DCP1) |
| **OND Division** | Division of Cardiovascular & Renal Products |
| **Sponsor** | EKR Therapeutics |
| **Dosage Form; Strength** | Injectable solution/ 0.2 mg/ml |
| **Proposed Indication** | Indicated for the short-term treatment of hypertension when oral therapy is not desirable |
| **Proposed Dosage Regimen** | Titration: Initiate therapy at 25 ml/hr (0.5 mg/hr). If desired effect is not achieved, increase infusion by 12.5 ml/hr (2.5 mg/hr) every 15 minutes up to a maximum of 75 ml/hr (15 mg/hr), until desired blood pressure reduction is achieved |
# CLINICAL PHARMACOLOGY REVIEW

## TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. EXECUTIVE SUMMARY</td>
<td>3</td>
</tr>
<tr>
<td>1.1 Recommendations</td>
<td>3</td>
</tr>
<tr>
<td>1.2 Phase IV Commitments</td>
<td>4</td>
</tr>
<tr>
<td>1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings</td>
<td>4</td>
</tr>
<tr>
<td>2. QUESTION BASED REVIEW</td>
<td>5</td>
</tr>
<tr>
<td>3. LABELING RECOMMENDATIONS</td>
<td>5</td>
</tr>
<tr>
<td>4. APPENDICES</td>
<td>5</td>
</tr>
<tr>
<td>4.1 Proposed Package Insert</td>
<td>6</td>
</tr>
<tr>
<td>4.2 Individual Study Reviews</td>
<td>21</td>
</tr>
</tbody>
</table>
1. EXECUTIVE SUMMARY

Original NDA 19-732 for Cardene I.V. (25 mg/10 ml ampul) was approved by FDA on January 30, 1992. Cardene I.V. (nicardipine hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium channel blocker) indicated for the short-term treatment of hypertension when oral therapy is not feasible or desirable.

It should be noted that the cover letter of this submission describes this supplement as a “PAS - Prior Approval Supplement”; however, FDA’s Document Room classified this submission as a “SCF - Formulation Change Supplement”. This supplement (SCF-014) to NDA 19-734 for Cardene I.V. provides for; 1) a new container closure system for Cardene I.V. and 2) an increase in concentration of the nicardipine hydrochloride concentration from 0.1 mg/mL to 0.2 mg/ml. The increased concentration of Cardene I.V. to 0.2 mg/ml is being supported by a bioequivalence (BE) study, which showed that this product is bioequivalent to the Cardene I.V. ampul product.

Currently, Cardene IV is available in ampuls at a concentration of 2.5mg/ml. Prior to administration, the ampul 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 will contain an increase in concentration from 0.1 mg/mL to 0.2 mg/ml of Cardene I.V. in a premixed dextrose or saline formulation in a ready to use presentation. It should be noted that the 0.1mg/ml concentration of Cardene I.V. in 4.8% dextrose in plastic container and Cardene I.V. (0.1 mg/ml) in 0.86% sodium chloride in plastic container were approved by the Agency under Supplement 013 on July 31, 2008.

In this supplement the sponsor mentions that upon approval of the 0.2 mg/ml labeling, they intend to combine the approved 0.1 mg/ml and 0.2 mg/ml package inserts into one document and also they intend to launch this new drug product with PDL BioPharma’s name until the new labeling can be supplied with EKR Therapeutics, Inc.’s name and logo (upon approval of this supplement, new labels will be ordered). Note that EKR assumed regulatory responsibility for Cardene I.V. from PDL BioPharma, Inc. on May 6, 2008.

1.1 RECOMMENDATION:

Bioequivalence:
The Office of Clinical Pharmacology/Division of Clinical Pharmacology I (OCPB/DCPI) has reviewed the overall information provided in NDA 19-734/SCF-014 dated May 14, 2008, for Cardene I.V. The results of the bioequivalence study showed that the ampul and pre-mix bag products are bioequivalent; therefore, the sponsor’s request to increase the concentration of nicardipine HCl from 0.1 mg/ml to 0.2 mg/ml in Cardene I.V. in 4.8% dextrose or 0.86% sodium chloride is acceptable.

Labeling:
The proposed labeling does not include any revisions for the clinical pharmacology information included in the current labeling for the approved Cardene I.V. product. However, it should be noted
that the content and format of the labeling included in the supplement follows the old labeling version and is not consistent with the current FDA labeling Guidance. ("Guidance for Industry; Labeling for Human Prescription Drug and Biological Products - Implementing the New Content and Format Requirements"). Therefore, OCP recommends that EKR Therapeutics updates the labeling for Cardene I.V. according to the recommendations provided in the new labeling guidance.

1.2 Phase 4 Commitments
Not applicable.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Clinical Pharmacology:
Clinical pharmacology studies were not provided in this supplement.

Biopharmaceutics:
**Bioequivalence Study (No.: Cardene IV 1407):** This study was a Phase 1, single-site, randomized, open label, 2-way crossover study conducted in 30 healthy men and women subjects. The study results showed that Cardene I.V. Double Strength (0.2 mg/ml) Premixed Injection is bioequivalent to the Cardene I.V. ampul product with respect to nicardipine Cmax, AUC_{\text{Cmax}}, and AUC_{\text{inf}}.

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>N</th>
<th>Test (Pre-MixBag)/Reference (Ampul)*</th>
<th>90% Confidence Interval$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>26</td>
<td>0.989</td>
<td>(94 - 106)</td>
</tr>
<tr>
<td>AUC_{\text{Cmax}} (ng*hr/ml)</td>
<td>26</td>
<td>0.979</td>
<td>(92 - 103)</td>
</tr>
<tr>
<td>AUC_{\text{inf}} (ng*hr/ml)</td>
<td>24</td>
<td>0.955</td>
<td>(92 - 100)</td>
</tr>
</tbody>
</table>

a. Ratio of geometric means of the parameter for the two treatments
b. 90% confidence interval for ratio of geometric means of the two treatment groups (as %).

A review of the bioequivalence study is included in the Appendix 4.2 (page 21).

Angelica Dorantes, Ph.D.
Division of Clinical Pharmacology I
Office of Clinical Pharmacology

FT signed by Robert Kumi, Ph.D. (Acting Team Leader)
cc: NDA 19-734/SCF-014, HFD-110, HFD-860 (Dorantes, Mehta, Uppoor)
2. **QUESTION BASED REVIEW**  
   A question based review section was not deemed necessary for this submission.

3. **DETAILED LABELING RECOMMENDATION**  
The proposed labeling for Cardene I.V. is included in Appendix 1 (Section 4.1 - Attachment 1). The April 2008-revised labeling version that is provided in this supplement did not change the clinical pharmacology information that is currently included in the approved labeling for this product. Therefore, there are no detailed comments for the revised version of the labeling included in Supplement SCF-014 to NDA 19-734.

4. **APPENDICES**  
   4.1 Proposed Labeling (see page 6 of this submission)  
   4.2 Individual Study Review (see page 21 of this submission)
APPENDIX 4.1

Includes:

NDA 19-734/SCF-014

Proposed Labeling
APPENDIX 4.2

Includes:

NDA 19-734/SCP 014

Review of Bioequivalence study Cardene® I.V. 1407
CLINICAL STUDY REPORT

**Study No.:** Cardene I.V. 1407

**Study Title:** Randomized, Open-label, Crossover, Bioequivalence Study of Cardene I.V. Double Strength Premixed Injection in Healthy Volunteers

**Investigator/Study Site:** Stephen D. Flach, MD, PhD, Medical Director Clinical Pharmacology, Covance Clinical Research Unit Inc. Madison, Wisconsin, USA

**Study Objectives:**
- **Primary:** To determine the bioequivalence of Cardene I.V. Double Strength Premixed Injection (nicardipine hydrochloride; 0.2 mg/ml) in 5% dextrose (test drug) and the currently approved Cardene I.V. ampul product (reference drug; diluted to 0.1 mg/ml in 5% dextrose in water) with respect to maximum plasma drug concentration and area under the concentration curve assessed to the last measured concentration.
- **Secondary:** To determine the safety and tolerability of Cardene I.V. Double Strength Premixed Injection (nicardipine hydrochloride; 0.2 mg/ml) in 5% dextrose.

**Study Design:**
Phase I, single-site, randomized, open label, 2-way crossover study to evaluate the bioequivalence of 2 formulations of Cardene I.V. in healthy men and women. Up to 30 subjects meeting the inclusion/exclusion criteria were planned; 30 subjects were enrolled; 27 subjects completed the study. The study design is presented below.

<table>
<thead>
<tr>
<th>Treatment Sequence</th>
<th>N*</th>
<th>Period 1</th>
<th>Washout</th>
<th>Period 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/B Up to 15</td>
<td></td>
<td>Treatment A: Test Drug. One hour infusion of Cardene I.V. double strength premixed injection at 0.2 mg/mL in 5% dextrose; Infusion rate: 25 mL/hour (5 mg/hour).</td>
<td>→</td>
<td>Treatment B: Reference Drug. One hour infusion of Cardene I.V. ampule product diluted to 0.1 mg/mL in D5W; Infusion rate: 50 mL/hour (5 mg/hour).</td>
</tr>
<tr>
<td>B/A Up to 15</td>
<td></td>
<td>Treatment B: Reference Drug. One hour infusion of Cardene I.V. ampule product diluted to 0.1 mg/mL in D5W; Infusion rate: 50 mL/hour (5 mg/hour).</td>
<td>→</td>
<td>Treatment A: Test Drug. One hour infusion of Cardene I.V. double strength premixed injection at 0.2 mg/mL in 5% dextrose; Infusion rate: 25 mL/hour (5 mg/hour).</td>
</tr>
</tbody>
</table>

2 DAYS 7-10 DAYS 2 DAYS

a. Up to 15 subjects per treatment sequence will be dosed in order to obtain at least 12 evaluable subjects in each treatment sequence.
Abbreviation: D5W = 5% dextrose in water solution.

The primary endpoint was the bioequivalence evaluation between the test drug and reference drug in the following pharmacokinetic parameters, subject to statistical comparison: 1) maximum plasma drug concentration and 2) area under the concentration curve assessed to the last measured concentration.

The secondary safety endpoints included: 1) Frequency, severity, and relatedness of adverse events and serious adverse events from enrollment through 48 hours after each infusion of study drug and 2) Study withdrawals due to adverse events from enrollment through 48 hours after each infusion of study drug.
**Study Drugs**

- **Test Drug:** Cardene I.V. Double Strength Premixed Injection (nicardipine hydrochloride; 0.2 mg/ml) in 5% dextrose (Lot No. NC042887) was administered as 5 mg/hour (25 ml/hour) intravenous (IV) infusion for 1 hour. The length of treatment (excluding screening) was approximately 2 weeks with 2 study visits including Treatment Period 1 (at least 49 hours), washout Period (7-10 days) and treatment Period 2 (at least 49 hours).

- **Reference Product:** Cardene I.V. approved ampul product (nicardipine hydrochloride; 25 mg in 10-mL ampuls for IV injection; Lot No. 087006) diluted to 0.1 mg/ml in dextrose in water (D5W) administered as 5 mg/hour (50 ml/hour) IV infusion for 1 hour.

The study treatments and their formulation are presented next.

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Dose Level and Frequency</th>
<th>Total No. Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment A: Test Drug</td>
<td>One hour infusion of Cardene I.V. Double Strength Premixed Injection at 0.2 mg/mL in 5% Dextrose; Infusion rate: 25 ml/hour (5 mg/hour).</td>
<td>1</td>
</tr>
<tr>
<td>Cardene I.V. Double Strength Premixed Injection in 5% Dextrose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment B: Reference Drug</td>
<td>One hour infusion of Cardene I.V. approved ampule product diluted to 0.1 mg/mL in D5W; (Infusion rate: 50 ml/hour (5 mg/hour).</td>
<td>1</td>
</tr>
<tr>
<td>Cardene I.V. approved ampule product</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Formulation Components**

<table>
<thead>
<tr>
<th>Component</th>
<th>Treatment A</th>
<th>Treatment B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicardipine hydrochloride (mg/mL)</td>
<td>0.20</td>
<td>0.10</td>
</tr>
<tr>
<td>Citric Acid (mg/mL)</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Sodium Hydroxide (mg/mL)</td>
<td>As needed to adjust pH</td>
<td>0.004</td>
</tr>
<tr>
<td>Citric or Hydrochloric Acid</td>
<td>As needed to adjust pH</td>
<td>As needed to adjust pH</td>
</tr>
<tr>
<td>Dextrose (mg/mL)</td>
<td>50</td>
<td>48</td>
</tr>
<tr>
<td>Sorbitol (mg/mL)</td>
<td>none</td>
<td>1.9</td>
</tr>
</tbody>
</table>

**Selection of the Doses**

The dose regimen of 5 mg/hour during a 1-hour infusion was used in the BE study due to the following reasons:

- According to the current label, the recommended regimen in adults is to initiate treatment at 5 mg/hour.
- Doses higher than 5 mg/hour may cause AEs such as decrease in blood pressure, headache, or tachycardia, which may result in early termination of subjects.

The following Figure shows the predicted concentration-time profile following a 1-hour constant infusion of Cardene I.V. at 5 mg/hour and an 80-hour elimination period. Pharmacokinetic simulation shows that the
area under the concentration-time curve from time 0 to 48 hours (AUC0-48) covers over 92% total AUC extrapolated to infinity (AUCinf), which is adequate for describing the total exposure. Therefore, a 1-hour constant infusion of Cardene I.V. followed by a 48-hour elimination period for PK sample collections was considered appropriate for comparing the PK profiles of the test vs. reference drugs.

Data Evaluation:

- **Analytical Method:** Plasma concentrations of nicardipine hydrochloride were determined using a validated LC/MS/MS method previously validated under (described in Technical Report TR06069). Cardene I.V. is a racemic mixture containing two enantiomers (+)S–nicardipine hydrochloride and (-)R–nicardipine hydrochloride. The R nicardipine and S nicardipine and the internal standard were extracted from human plasma by liquid extraction. After evaporation under nitrogen, the residue was reconstituted and analyzed using liquid chromatography (LC) with tandem mass spectrometric detection (MS/MS). Both nicardipine hydrochloride enantiomers are pharmacologically active. There is no documented difference between the nicardipine enantiomers with respect to protein binding or stereoselective hepatic metabolism of P450 enzymes. Studies have indicated that (+)–nicardipine hydrochloride is present at similar levels in serum than (-)–nicardipine hydrochloride after intravenous administration of the racemic mixture. The plasma concentrations of nicardipine racemic mixture were used to calculate the values of the standard PK parameters, including Cmax, AUClast, and AUCinf. The serum levels for both enantiomers are similar following intravenous administration.

- **Pharmacokinetics:** PK blood samples (approximately 4 ml) were collected at time 0 (predose), 5, 15, 30, 45, 60 (end of infusion), 65, 75 minutes, 1.5, 1.75, 2, 3, 4, 5, 6, 9, 12, 15, 18, 24, 36, and 48
hrs after the beginning of infusion periods 1 and 2. The concentration values represent the sum of S- and R-nicardipine isomers values.

Maximum plasma drug concentration (Cmax), Area under the concentration curve assessed to the last measured concentration (AUClast), AUC extrapolated to infinity (AUCinf). Pharmacokinetic parameters were estimated by non-compartmental analysis using WinNonlin. Plasma concentrations of the nicardipine racemic mixture, the calculated parameters of Cmax, AUClast, AUCinf, and apparent terminal phase elimination rate constant (λz) were presented by subject and treatment.

- **Bioequivalence:** Following loge-transformation, AUC0-t and Cmax of nicardipine were analyzed by analysis of variance (ANOVA) with terms for sequence, subject within sequence, period, and treatment. The point estimates and associated 90% confidence intervals for the ratio of the test treatment mean relative to the reference treatment mean were constructed using the residual variances.

- **Safety:** Physical examinations; vital signs; 12-lead electrocardiograms (ECGs); adverse event (AE) evaluations; clinical laboratory measurements to include blood chemistry, hematology, and urinalysis

**RESULTS:**

- **Pharmacokinetics:** The following tables summarize the pharmacokinetic results.

### Summary of the Arithmetic Mean (SD) Plasma Pharmacokinetic Parameter Data for Nicardipine

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>UNITS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Cmax</td>
<td>(ng/ml)</td>
<td>28</td>
</tr>
<tr>
<td>AUClast</td>
<td>(ng*hr/ml)</td>
<td>28</td>
</tr>
<tr>
<td>AUCinf</td>
<td>(ng*hr/ml)</td>
<td>28</td>
</tr>
<tr>
<td>AUClast/AUCinf</td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>λz</td>
<td>(1/hour)</td>
<td>28</td>
</tr>
</tbody>
</table>

### Summary of the Statistical Analysis of the Plasma Pharmacokinetic Parameter Data for Nicardipine

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>N</th>
<th>Test (Pre-Mix Bag)/Reference (Ampul)a</th>
<th>90% Confidence Intervalb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>26</td>
<td>99.9</td>
<td>(94 - 106)</td>
</tr>
<tr>
<td>AUClast (ng*hr/ml)</td>
<td>26</td>
<td>97.9</td>
<td>(92 - 103)</td>
</tr>
<tr>
<td>AUCinf (ng*hr/ml)</td>
<td>24</td>
<td>95.5</td>
<td>(92 - 100)</td>
</tr>
</tbody>
</table>

- **Parameter (units):**
  - Cmax: Maximum plasma drug concentration
  - AUClast: Area under the concentration curve assessed to the last measured concentration
  - AUCinf: Area under the concentration curve extrapolated to infinity
  - λz: Apparent terminal phase elimination rate constant

**Abbreviations:**
- Cmax: Maximum plasma drug concentration
- AUClast: Area under the concentration curve assessed to the last measured concentration
- AUCinf: Area under the concentration curve extrapolated to infinity
- λz: Apparent terminal phase elimination rate constant
- N: Number of subjects
- SD: Standard deviation
The 90% confidence intervals for the comparison of total racemic nicardipine Cmax, AUClast, and AUClinf between the pre-mix bag and ampul formulations were within the Agency’s acceptance criteria of 80% to 125%, indicating bioequivalence.

- **Safety:** All subjects who completed study dosing were administered a total of 5 mg during both Treatment A and Treatment B. Three (Sequence A/B) of the 30 subjects did not complete the study. Subject No. 108 was withdrawn at Period 2 Check-in for abnormal laboratory values (3 clinically significant hepatic values). Subject No. 109 was withdrawn during dosing on Period 1, Day 1, for moderate, related AEs of tachycardia and anxiety. Subject No. 110 withdrew consent postdose on Period 1, Day 2. No deaths or serious adverse events (SAEs) were reported during this study. The most common AEs reported overall (at least 3 subjects) included dizziness, ecchymosis, flushing, and headache. The most common related, reported AEs (at least 3 subjects) included dizziness (4 mild and 2 moderate), flushing (9 mild), and headache (10 mild). Most of these events were expected consequences of vasodilation.

**Reviewer Comments:**
1. OCP considers that the approach used by the sponsor (based on the drug’s safety information and PK-simulated data) for the selection of the dose regimen of 5 mg/hour during a 1-hour infusion is acceptable.
2. The LC/MS/MS analytical method that was used to assay nicardipine racemic mixture containing the two enantiomers (R-nicardipine and S-nicardipine) was properly validated and it is acceptable.
3. The results of the BE study show that the Cardene I.V. double strength (0.2 mg/ml) premixed injection is bioequivalent to the Cardene I.V. ampul product. Therefore, the sponsor’s request to increase the concentration of nicardipine HCl from 0.1 ng/ml to 0.2 mg/ml in Cardene I.V. in either 4.8% dextrose or 0.86% sodium chloride is acceptable.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Angelica Dorantes
9/24/2008 12:36:07 PM
BIOPHARMACEUTICS

Robert Kumi
9/24/2008 12:58:18 PM
BIOPHARMACEUTICS
REQUEST FOR CONSULTATION

TO: DMETS
Mail: ODS

FROM: Lori Wachter Regulatory Health Project Manager,
Division of Cardiovascular and Renal Product

DATE: September 22, 2008
IND NO.: NDA NO. 19-734
NAME OF DRUG: Nicardipine Hydrochloride
NAME OF FIRM: EKR

NAME OF PHARMACEUTICAL PRODUCT: Nicardipine Hydrochloride

PRIORITY CONSIDERATION: Calcium Channel Blocker

DATE OF DOCUMENT: October 14, 2008

REASON FOR REQUEST

I. GENERAL

- NEW PROTOCOL
- PROGRESS REPORT
- NEW CORRESPONDENCE
- DRUG ADVERTISING
- ADVERSE REACTION REPORT
- MANUFACTURING CHANGE/ADDITION
- MEETING PLANNED BY
- PRE-nda MEETING
- END OF PHASE II MEETING
- RESUBMISSION
- SAFETY/EFFICACY
- PAPER NDA
- CONTROL SUPPLEMENT
- RESPONSE TO DEFICIENCY LETTER
- FINAL PRINTED LABELING
- LABELING REVISION
- ORIGINAL NEW CORRESPONDENCE
- FORMULATIVE REVIEW
- OTHER (SPECIFY BELOW):

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- TYPE A OR B NDA REVIEW
- END OF PHASE II MEETING
- CONTROLLED STUDIES
- PROTOCOL REVIEW
- OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

- CHEMISTRY REVIEW
- PHARMACOLOGY
- BIOPHARMACEUTICS
- OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES
- DEFICIENCY LETTER RESPONSE
- PROTOCOL-BIOPHARMACEUTICS
- IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DiAGNOSSES
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- CLINICAL
- PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: This application has been submitted as a labeling change with an increase in concentration of the drug. The company will now have a 1X and a 2X version of their product. There is a concern over possible confusion between the labels. The sponsor has addressed this with different color labels (black for 1X and red for 2X) however the concern still exists. We are attaching the carton, container, and bag labels.

This application was NOT submitted electronically and the SPL will be submitted shortly.

SIGNATURE OF REQUESTER

Lori Wachter

METHOD OF DELIVERY (Check one)

X MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

8 Page(s) have been Withheld in Full as Draft Labeling immediately following this page.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

---------------------
Lori Wachter
9/23/2008 11:02:48 AM
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. 19-734

NDA NO.

TYPE OF DOCUMENT SCF-014

DATE OF DOCUMENT May 15, 2008

NAME OF DRUG Cardene

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE August 15, 2008

NAME OF FIRM: EKR Therap

REASON FOR REQUEST

I. GENERAL

- NEW PROTOCOL
- PROGRESS REPORT
- NEW CORRESPONDENCE
- DRUG ADVERTISING
- ADVERSE REACTION REPORT
- MANUFACTURING CHANGE / ADDITION
- MEETING PLANNED BY

- PRE-NDA MEETING
- END-OF-PHASE 2a MEETING
- END-OF-PHASE 2 MEETING
- RESUBMISSION
- SAFETY / EFFICACY
- PAPER NDA
- CONTROL SUPPLEMENT

- RESPONSE TO DEFICIENCY LETTER
- FINAL PRINTED LABELING
- LABELING REVISION
- ORIGINAL NEW CORRESPONDENCE
- FORMULATIVE REVIEW
- OTHER (SPECIFY BELOW):

II. BIOMETRICS

- PRIORITY P NDA REVIEW
- END-OF-PHASE 2 MEETING
- CONTROLLED STUDIES
- PROTOCOL REVIEW
- OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
- PHARMACOLOGY
- BIOPHARMACEUTICS
- OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
- BIOAVAILABILITY STUDIES
- PHASE 4 STUDIES

- DEFICIENCY LETTER RESPONSE
- PROTOCOL - BIOPHARMACEUTICS
- IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- PHASE 4 SURVEILLANCE/Epidemiology protocol
- DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- CLINICAL
- NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This supplement provides for a new container closure system and increased in concentration of Nicardipine Hydrochloride to 0.2 mg/mL. Please review.

PDUFA Goal date: September 15, 2008

SIGNATURE OF REQUESTOR
Teshara G. Bouie

METHOD OF DELIVERY (Check one)
✓ DFS   ☐ EMAIL   ☐ MAIL   ☐ HAND

PRINTED NAME AND SIGNATURE OF DELIVERER

PRINTED NAME AND SIGNATURE OF RECEIVER
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

---------------------
Teshara Bouie
6/12/2008 04:49:32 PM
NDA 19-734/S-014

PRIOR APPROVAL SUPPLEMENT

EKR Therapeutics, Inc.
Attention: Alex Mironov
Director, Regulatory Affairs
1545 Route 206
Bedminster, NJ 07921

Dear Mr. Mironov:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Cardene® I.V. (nicardipine hydrochloride)

NDA Number: 19-734

Supplement number: S-014

Date of supplement: May 14, 2008

Date of receipt: May 15, 2008

This supplemental application proposes the addition of new container closure system for the Cardene I.V. drug product and an increase in concentration of the nicardipine hydrochloride concentration to 0.2 mg/mL.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 14, 2008 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 14, 2008.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266
If you have questions, please contact:

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

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
-------------------------------
Russell Fortney
6/23/2008 10:38:58 AM
Signing for Edward Fromm