



NDA 019734/S-015

SUPPLEMENT APPROVAL

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

Dear Mr. Mironov:

Please refer to your supplemental new drug application dated March 16, 2009, received March 17, 2009, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Cardene (nicardipine hydrochloride) 0.1 mg/ml and 0.2 mg/ml Premixed Injection.

This "Prior Approval" supplemental new drug application provides for conversion of the label to the Physicians Labeling Rule (PLR) Format. The following changes were proposed:

1. In **HIGHLIGHTS/DOSAGE AND ADMINISTRATION**, the word "below" has been added to the third bullet. The sentence now reads:

When substituting for oral nicardipine therapy, use the intravenous infusion rate from the table below:

2. In **HIGHLIGHTS/DOSAGE AND ADMINISTRATION**, the fourth bullet has been changed from:

In a patient not receiving nicardipine, initiate therapy at 50 mL/hr (5 mg/hr). Increase the infusion rate by 25 mL/hr every 5 minutes to 15 minutes up to a maximum of 150 mL/hr until desired blood pressure reduction is achieved. (2.4)

To:

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)

3. In **FULL PRESCRIBING INFORMATION/WARNINGS AND PRECAUTIONS**, 5.1 has been changed from:

Excessive Pharmacologic Effects

To:

Excessive Pharmacodynamic Effects

4. In **FULL PRESCRIBING INFORMATION/WARNINGS AND PRECAUTIONS**, 5.2 “Rapid Decreases in Blood Pressure” has been deleted.
5. In **FULL PRESCRIBING INFORMATION/WARNINGS AND PRECAUTIONS**, 5.3 the word “Congestive” has been deleted. The heading now reads:

Use in Patients with Heart Failure

6. In **FULL PRESCRIBING INFORMATION/WARNINGS AND PRECAUTIONS**, 5.7 “Beta Blocker Withdrawal” has been deleted.
7. In **FULL PRESCRIBING INFORMATION/WARNINGS AND PRECAUTIONS**, 5.8 “Use in Patients with Pheochromocytoma” has been deleted.
8. In **INDICATIONS AND USAGE**, the words “(nicardipine hydrochloride) Premixed Injection” have been added to the first sentence of the first paragraph. The sentence now reads:

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.

9. In **DOSAGE AND ADMINISTRATION/Recommended Dosing**, the first paragraph has been changed from:

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

To:

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

10. In **DOSAGE AND ADMINISTRATION/Recommended Dosing**, the dosage substitution table has been changed from:

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

To:

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

11. In **DOSAGE AND ADMINISTRATION/Recommended Dosing**, the fifth paragraph has been changed from:

For Initiation of Therapy in a Drug Free Patient

The time course of blood pressure decrease is dependent on the initial rate of infusion and the frequency of dosage adjustment. Cardene I.V. is administered by slow continuous infusion at a CONCENTRATION OF 0.1 MG/ML. With constant infusion, blood pressure begins to fall within minutes. It reaches about 50% of its ultimate decrease in about 45 minutes and does not reach final steady state for about 50 hours.

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

Titration: For gradual reduction in blood pressure, initiate therapy at 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 15 minutes up to a maximum of 150 mL/hr (15.0 mg/hr), until desired blood pressure reduction is achieved.

For more rapid blood pressure reduction, 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 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, the infusion rate should be decreased to 30 mL/hr (3 mg/hr).

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

To:

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).

12. In **DOSAGE AND ADMINISTRATION/Recommended Dosing**, the seventh paragraph has been changed from:

TRANSFER TO ORAL ANTIHYPERTENSIVE AGENTS

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

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

To:

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.

13. In **DOSAGE AND ADMINISTRATION/Recommended Dosing**, the following has been added:

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)*]

14. In **DOSAGE AND ADMINISTRATION/Monitoring**, the first paragraph has been changed from:

The time course of blood pressure decrease is dependent on the initial rate of infusion and the frequency of dosage adjustment. Cardene I.V. is administered by slow continuous infusion at a CONCENTRATION OF 0.1 MG/ML. With constant infusion, blood pressure begins to fall within minutes. It reaches about 50% of its ultimate decrease in about 45 minutes and does not reach final steady state for about 50 hours.

To:

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.

15. In **DOSAGE AND ADMINISTRATION/Monitoring**, the sentence: “Monitor blood pressure and heart rate continually during infusion and avoid too rapid or excessive blood pressure drop during treatment.” has been added as the first sentence of the second paragraph.
16. In **DOSAGE AND ADMINISTRATION/Instructions for Administration/Preparation for administration**, the word “plastic” has been deleted from the second sentence. The sentence now reads:

Remove protector from outlet port at bottom of container.

17. In **CONTRAINDICATIONS**, the following has been deleted:

4.1 Hypersensitivity

Cardene I.V. Premixed Injection is contraindicated in patients with known hypersensitivity to the drug.

18. In **CONTRAINDICATIONS/Advanced Aortic Stenosis**, the words “Premixed Injection” have been added to the first sentence of the first paragraph. The sentence now reads:

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.

19. In **WARNINGS AND PRECAUTIONS/Excessive Pharmacodynamic Effects**, the first paragraph has been changed from:

Blood Pressure: Because Cardene I.V. decreases peripheral resistance, monitoring of blood pressure during administration is required. Cardene I.V., like other calcium channel blockers, may occasionally produce symptomatic hypotension. Caution is advised to avoid systemic hypotension when administering the drug to patients who have sustained an acute cerebral infarction or hemorrhage.

To:

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.

20. In **WARNINGS AND PRECAUTIONS/Use in Patients with Angina**, the words “oral nicardipine” replace the words “Cardene capsule”. The first sentence of the first paragraph now reads:

Increases in frequency, duration, or severity of angina have been seen in chronic therapy with oral nicardipine.

21. In **WARNINGS AND PRECAUTIONS/Use in Patients with Heart Failure**, the first paragraph has been changed from:

USE IN PATIENTS WITH CONGESTIVE HEART FAILURE

Cardene I.V. reduced afterload without impairing myocardial contractility in preliminary hemodynamic studies of CHF patients. However, in vitro and in some patients, a negative inotropic effect has been observed. Therefore, caution should be exercised when using Cardene I.V., particularly in combination with a beta-blocker, in patients with CHF or significant left ventricular dysfunction.

To:

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.

22. In **WARNINGS AND PRECAUTIONS/Use in Patients with Impaired Hepatic Function**, the first paragraph has been changed from:

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

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

To:

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.

23. In **WARNINGS AND PRECUTIONS/Use in Patients with Impaired Renal Function**, the first paragraph has been changed from:

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

To:

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.

24. In **ADVERSE REACTIONS/Adverse Reactions Observed in Clinical Trials**, the following text has been added as the first paragraph:

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.

25. In **ADVERSE REACTIONS/Adverse Reactions Observed in Clinical Trials**, the word “on” has been deleted from the third paragraph. The paragraph now reads:

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

26. In **ADVERSE REACTIONS/Adverse Reactions Observed in Clinical Trials**, the Adverse Event table has been shortened. The table now appears:

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

27. In **ADVERSE REACTIONS/Adverse Reactions Observed in Clinical Trials**, the following text now appears under the Adverse Event table:

“Other adverse events have been reported in clinical trials or in the literature in association with the use of intravenously administered nicardipine:”

28. In **DRUG INTERACTIONS/Beta-Blockers**, the second sentence of the first paragraph has been changed from:

However, caution should be exercised when using Cardene I.V. in combination with a beta-blocker in congestive heart failure patients (see “Warnings”).

To:

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)*].

29. In **DRUG INTERACTIONS/Cimetidine**, the first paragraph has been changed from:

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

To:

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.

30. In **USE IN SPECIFIC POPULATIONS/Pregnancy**, the section has been changed from:

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

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

To:

There are no adequate and well-controlled studies of nicardipine use in pregnant women. However, limited human data in pregnant women with preeclampsia or pre-term labor are available. In animal studies, no embryotoxicity occurred in rats with oral doses 8 times the maximum recommended human dose (MRHD) based on body surface area (mg/m^2), but did occur in rabbits with oral doses at 24 times the maximum recommended human dose (MRHD) based on body surface area (mg/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 (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^2) (5 mg/kg/day) (rats) and 0.03 times the MRHD based on body surface area (mg/m^2) (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^2) (10 mg/kg/day) in rats and at 0.05 times the MRHD based on body surface area (mg/m^2) (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^2) (50 and 150 mg/kg/day). Embryotoxicity occurred at the high dose along with signs of maternal toxicity (marked maternal weight gain suppression). New Zealand albino rabbits received oral nicardipine during organogenesis, at doses up to 16 times the MRHD based on body surface area (mg/m^2) (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^2) (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.

31. In **USE IN SPECIFIC POPULATIONS/Nursing Mothers**, the section has been changed from:

Studies in rats have shown significant concentrations of nicardipine in maternal milk. For this reason, it is recommended that women who wish to breastfeed should not be given this drug.

To:

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.

32. In **OVERDOSAGE**, the second sentence was changed from:

One adult patient allegedly ingested 600 mg of nicardipine immediate release capsules, and another patient, 2160 mg of the sustained release formulation of nicardipine.

To:

One adult patient allegedly ingested 600 mg of immediate release oral nicardipine, and another patient, 2160 mg of the sustained release formulation of nicardipine.

33. In **DESCRIPTION/Cardene I.V. Premixed Injection in 0.86% Sodium Chloride**, the first sentence of the second paragraph was changed from:

The GALAXY plastic container is fabricated from a specially designed multilayered plastic (PL 2501).

To:

The GALAXY container is fabricated from multilayered plastic (PL 2501).

34. In **NONCLINICAL TOXICOLOGY/Carcinogenesis, Mutagenesis, Impairment of Fertility**, the fifth paragraph has been changed from:

In pregnant rats administered nicardipine orally at up to 100 mg/kg/day (50 times the maximum recommended human dose) there was no evidence of embryoletality or teratogenicity.

To:

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).

35. In **NONCLINICAL TOXICOLOGY/Reproductive and Developmental Toxicology**, the fourth sentence in the first paragraph has been changed from:

Nicardipine was embryocidal when administered orally to pregnant Japanese White rabbits, during organogenesis, at 150 mg/kg/day (a dose associated with marked body weight gain suppression in the treated doe), but not at 50 mg/kg/day (25 times the maximum recommended dose in man).

To:

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).

36. In **HOW SUPPLIED/STORAGE AND HANDLING**, the following text has been added:

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

37. The words “oral nicardipine” have replaced “Cardene capsules” throughout the label.

There are no other changes from the last approved package insert.

We have completed our review of this application and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed upon labeling text.

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(1)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the package insert). For administrative purposes, please designate this submission, “SPL for approved NDA 019734/S-015.

LETTERS TO HEALTH CARE PROFESSIONALS

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

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

REPORTING REQUIREMENTS

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 Anne Wachter, RN, BSN
Regulatory Project Manager
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, Pharm.D.
Deputy Director for Safety
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Agreed-upon labeling text

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-19734	SUPPL-15	EKR THERAPEUTICS INC	CARDENE (NICARDIPINE HCL) INJ

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

/s/

MARY R SOUTHWORTH
01/13/2010