CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

019734Orig1s014

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.

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019734Orig1s014

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019734Orig1s014

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019734Orig1s014

LABELING

CARDENE® I.V.
(nicardipine hydrochloride)

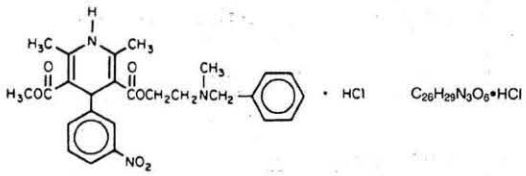
Premixed Injection in either 4.8% Dextrose or 0.86% Sodium Chloride

*BAR CODE LOCATION ONLY
71955613

Rx only

Description

Cardene® (nicardipine HCl) 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 (±)-2-(benzyl-methyl amino) ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate monohydrochloride and has the following structure:



$C_{26}H_{29}N_3O_6 \cdot HCl$

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 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.

Clinical Pharmacology

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.

PHARMACOKINETICS AND METABOLISM

Following infusion, nicardipine plasma concentrations decline tri-exponentially, with a rapid early distribution phase (α-half-life of 2.7 minutes), an intermediate phase (β-half-life of 44.8 minutes), and a slow terminal phase (γ-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.

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. 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.

Cardene I.V. has been shown to be rapidly and extensively metabolized by the liver. 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.

Nicardipine does not induce or inhibit its own metabolism and does not induce or inhibit hepatic microsomal enzymes.

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

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 ± 1 bpm in postoperative patients and 8 ± 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 Cardene capsules. 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 nicardipine is extensively metabolized by the liver, plasma concentrations are influenced by changes in hepatic function. In a clinical study with Cardene capsules in patients with severe liver disease, plasma concentrations were elevated and the half-life was prolonged (see "**Precautions**"). 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 Cardene capsules (20 mg or 30 mg TID) were 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 "**Precautions**").

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, Cardene capsules (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 Cardene capsules, no evidence of increased bronchospasm was seen. In one of the studies, Cardene capsules improved forced expiratory volume 1 second (FEV_1) 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 Cardene capsules.

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, although only the decreases at 4.0 mg/hr were statistically different from placebo. 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 ≤95 mmHg or ≥25 mmHg decrease and systolic blood pressure ≤160 mmHg, was 77 ± 5.2 minutes. The average maintenance dose was 8.0 mg/hr. The mean time to therapeutic response for postoperative hypertension, defined as ≥15% reduction in diastolic or systolic blood pressure, was 11.5 ± 0.8 minutes. The average maintenance dose was 3.0 mg/hr.

Indication and Usage

Cardene I.V. is indicated for the short-term treatment of hypertension when oral therapy is not feasible or not desirable.

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

Warnings

BETA-BLOCKER WITHDRAWAL

Nicardipine is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of dose of beta-blocker.

RAPID DECREASES IN BLOOD PRESSURE

No clinical events have been reported suggestive of a too rapid decrease in blood pressure with Cardene I.V. However, as with any antihypertensive agent, blood pressure lowering should be accomplished over as long a time as is compatible with the patient's clinical status.

USE IN PATIENTS WITH ANGINA

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

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.

USE IN PATIENTS WITH PHEOCHROMOCYTOMA

Only limited clinical experience exists in use of Cardene I.V. for patients with hypertension associated with pheochromocytoma. Caution should therefore be exercised when using the drug in these patients.

PERIPHERAL VEIN INFUSION SITE

To minimize the risk of peripheral venous irritation, it is recommended that the site of infusion of Cardene I.V. be changed every 12 hours.

Precautions

GENERAL

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.

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

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

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

DRUG INTERACTIONS

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

BETA-BLOCKERS

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

CIMETIDINE

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

DIGOXIN

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

FENTANYL ANESTHESIA

Hypotension has been reported during fentanyl anesthesia with concomitant use of a beta-blocker and a calcium channel blocker. Even though such interactions were not seen during clinical studies with Cardene I.V. (nicardipine hydrochloride), an increased volume of circulating fluids might be required if such an interaction were to occur.

CYCLOSPORINE

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

IN VITRO INTERACTION

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

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Rats treated with nicardipine in the diet (at concentrations calculated to provide daily dosage levels of 5, 15, or 45 mg/kg/day) for two years showed a dose-dependent increase in thyroid hyperplasia and neoplasia (follicular adenoma/carcinoma). One- and three-month studies in the rat have suggested that these results are linked to a nicardipine-induced reduction in plasma thyroxine (T4) levels with a consequent increase in plasma levels of thyroid stimulating hormone (TSH). Chronic elevation of TSH is known to cause hyperstimulation of the thyroid. In rats on an iodine deficient diet, nicardipine administration for one month was associated with thyroid hyperplasia that was prevented by T4 supplementation. Mice treated with nicardipine in the diet (at concentrations calculated to provide daily dosage levels of up to 100 mg/kg/day) for up to 18 months showed no evidence of neoplasia of any tissue and no evidence of thyroid changes. There was no evidence of thyroid pathology in dogs treated with up to 25 mg nicardipine/kg/day for one year and no evidence of effects of nicardipine on thyroid function (plasma T4 and TSH) in man. There was no evidence of a mutagenic potential of nicardipine in a battery of genotoxicity tests conducted on microbial indicator organisms, in micronucleus tests in mice and hamsters, or in a sister chromatid exchange study in hamsters. No impairment of fertility was seen in male or female rats administered nicardipine at oral doses as high as 100 mg/kg/day (50 times the 40 mg TID maximum recommended dose in man, assuming a patient weight of 60 kg).

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

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

NURSING MOTHERS

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

PEDIATRIC USE

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

GERIATRIC USE

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

Clinical studies of nicardipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Adverse Experiences

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

Percent of Patients with Adverse Experiences During the Double-Blind Portion of Controlled Trials

Adverse Experience	Cardene (n=144)	Placebo (n=100)
Body as a Whole		
Headache	14.6	2.0
Asthenia	0.7	0.0
Abdominal pain	0.7	0.0
Chest pain	0.7	0.0
Cardiovascular		
Hypotension	5.6	1.0
Tachycardia	3.5	0.0
ECG abnormality	1.4	0.0
Postural hypotension	1.4	0.0
Ventricular extrasystoles	1.4	0.0
Extrasystoles	0.7	0.0
Hemopericardium	0.7	0.0
Hypertension	0.7	0.0
Supraventricular tachycardia	0.7	0.0
Syncope	0.7	0.0
Vasodilation	0.7	0.0
Ventricular tachycardia	0.7	0.0
Digestive		
Nausea/vomiting	4.9	1.0
Injection Site		
Injection site reaction	1.4	0.0
Injection site pain	0.7	0.0
Metabolic and Nutritional		
Hypokalemia	0.7	0.0
Nervous		
Dizziness	1.4	0.0
Hypesthesia	0.7	0.0
Intracranial hemorrhage	0.7	0.0
Paresthesia	0.7	0.0
Respiratory		
Dyspnea	0.7	0.0
Skin and Appendages		
Sweating	1.4	0.0
Urogenital		
Polyuria	1.4	0.0
Hematuria	0.7	0.0

RARE EVENTS

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

Body as a Whole: fever, neck pain

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

Digestive: dyspepsia

Hemic and Lymphatic: thrombocytopenia

Metabolic and Nutritional: hypophosphatemia, peripheral edema

Nervous: confusion, hypertonia

Respiratory: respiratory disorder

Special Senses: conjunctivitis, ear disorder, tinnitus

Urogenital: urinary frequency

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

Overdosage

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

Based on results obtained in laboratory animals, lethal overdose may cause systemic hypotension, bradycardia (following initial tachycardia) and progressive atrioventricular conduction block. Reversible hepatic function abnormalities and sporadic focal hepatic necrosis were noted in some animal species receiving very large doses of nicardipine.

For treatment of overdosage, standard measures including monitoring of cardiac and respiratory functions should be implemented. The patient should be positioned so as to avoid cerebral anoxia. Frequent blood pressure determinations are essential. Vasopressors are clinically indicated for patients exhibiting profound hypotension. Intravenous calcium gluconate may help reverse the effects of calcium entry blockade.

Dosage and Administration

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

PREPARATION

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

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

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

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

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

Preparation for administration:

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.

DOSAGE

As a Substitute for Oral Nicardipine Therapy

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

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

For Initiation of Therapy in a Drug Free Patient

The time course of blood pressure decrease is dependent on the initial rate of infusion and the frequency of dosage adjustment. Cardene I.V. is administered by slow continuous infusion at a CONCENTRATION OF 0.1 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.

CONDITIONS REQUIRING INFUSION ADJUSTMENT

Hypotension or Tachycardia: If there is concern of impending hypotension or tachycardia, the infusion should be discontinued. When blood pressure has stabilized, infusion of Cardene I.V. may be restarted at low doses such as 30 - 50 mL/hr (3.0 - 5.0 mg/hr) and adjusted to maintain desired blood pressure.

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

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

TRANSFER TO ORAL ANTIHYPERTENSIVE AGENTS

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

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

How Supplied

Cardene I.V. premixed injection is supplied as a single-use, ready-to-use, iso-osmotic solution for intravenous administration in 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® I.V. is a registered trademark of PDL BioPharma Inc.
Baxter and GALAXY are registered trademarks of Baxter International Inc.

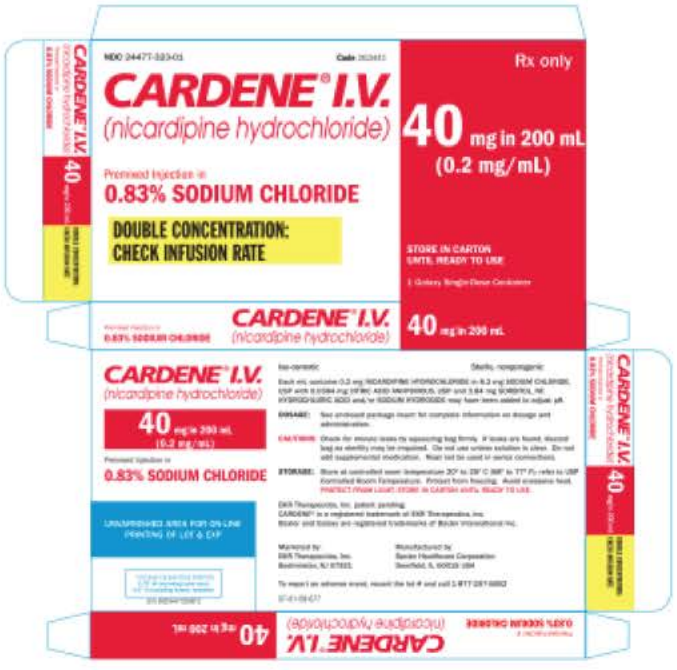
To report an adverse event, record the lot number and call Drug Safety at 1-866-437-7742
Revised March 2008

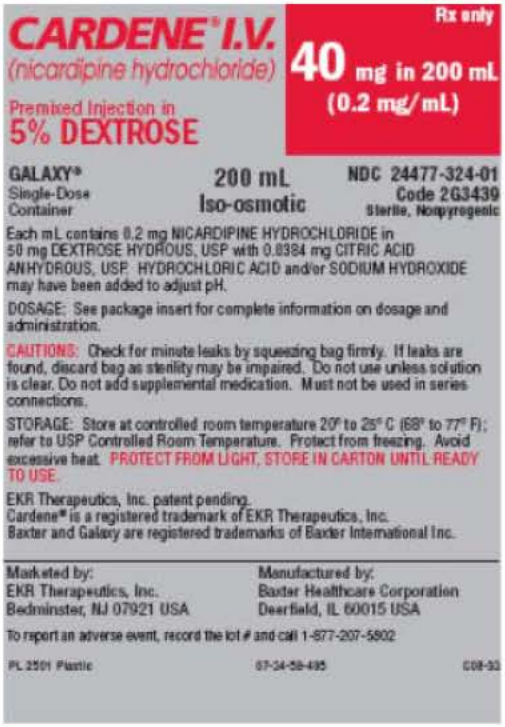
07-19-55-613 161301

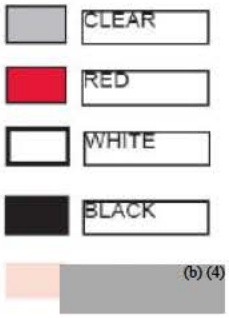
Manufactured by:
Baxter Healthcare Corporation
Deerfield, IL 60015 USA

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


NDC 24477-324-01
Code 203439
CARDENE® I.V.
(nicardipine hydrochloride)
Premixed Injection in
5% DEXTROSE
DOUBLE CONCENTRATION:
CHECK INFUSION RATE
Rx only
40 mg in 200 mL
(0.2 mg/mL)
STORE IN CARTON
UNTIL READY TO USE
1 Galaxy Single-Dose Container
40 mg in 200 mL
Non-sterile
Sterile, nonpyrogenic
Each mL contains 0.2 mg NICARDIPINE HYDROCHLORIDE in 50 mg DEXTROSE HYDROUS, USP with 0.0364 mg CITRIC ACID ANHYDROUS, USP; HYDROCHLORIC ACID and/or SODIUM HYDROXIDE may have been added to adjust pH.
DOSAGE:
CAUTION:
STORAGE:
UNVARNISHED AREA FOR ON-LINE PRINTING OF LOT & EXP
EKR Therapeutics, Inc. patent pending
CARDENE® is a registered trademark of EKR Therapeutics, Inc.
Baxter and Galaxy are registered trademarks of Baxter International Inc.
Marketed by:
EKR Therapeutics, Inc.
Bedminster, NJ 07921 USA
Manufactured by:
Baxter Healthcare Corporation
Deerfield, IL 60015 USA
To report an adverse event, record the lot # and call 1-877-207-5803
07-01-58-621
008-99


CARDENE® I.V.
(nicardipine hydrochloride)
Premixed Injection in
0.83% SODIUM CHLORIDE
DOUBLE CONCENTRATION:
CHECK INFUSION RATE
Rx only
40 mg in 200 mL
(0.2 mg/mL)
STORE IN CARTON
UNTIL READY TO USE
40 mg in 200 mL


CARDENE® I.V.
(nicardipine hydrochloride)
Premixed Injection in
5% DEXTROSE
Rx only
40 mg in 200 mL
(0.2 mg/mL)
GALAXY®
Single-Dose
Container
200 mL
Iso-osmotic
NDC 24477-324-01
Code 2G3439
Sterile, Nonpyrogenic
Each mL contains 0.2 mg NICARDIPINE HYDROCHLORIDE in
50 mg DEXTROSE HYDROUS, USP with 0.0384 mg CITRIC ACID
ANHYDROUS, USP. HYDROCHLORIC ACID and/or SODIUM HYDROXIDE
may have been added to adjust pH.
DOSAGE: See package insert for complete information on dosage and
administration.
CAUTIONS: Check for minute leaks by squeezing bag firmly. If leaks are
found, discard bag as sterility may be impaired. Do not use unless solution
is clear. Do not add supplemental medication. Must not be used in series
connections.
STORAGE: 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.
EKR Therapeutics, Inc. patent pending.
Cardene® is a registered trademark of EKR Therapeutics, Inc.
Baxter and Galaxy are registered trademarks of Baxter International Inc.
Marketed by:
EKR Therapeutics, Inc.
Bedminster, NJ 07921 USA
Manufactured by:
Baxter Healthcare Corporation
Deerfield, IL 60015 USA
To report an adverse event, record the lot # and call 1-877-207-5802
PL 2501 Plastic
07-34-58-495
C08-33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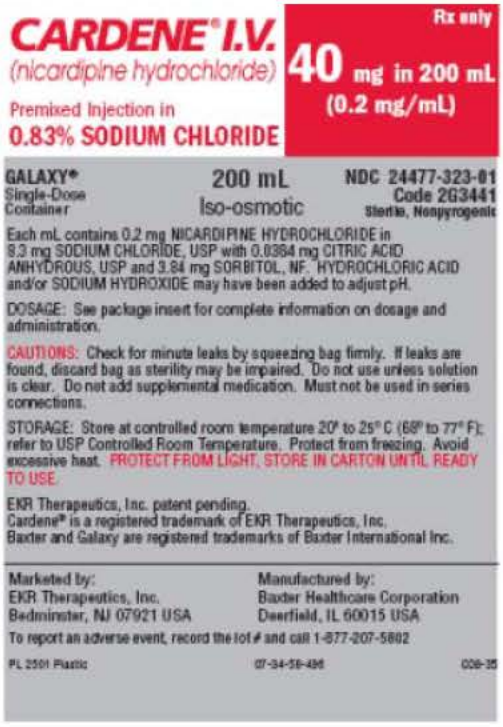
CARDENE® I.V.
(nicardipine hydrochloride)
Premixed Injection in
0.83% SODIUM CHLORIDE
Rx only
40 mg in 200 mL
(0.2 mg/mL)
GALAXY®
Single-Dose
Container
200 mL
Iso-osmotic
NDC 24477-323-01
Code 2G3441
Sterile, Nonpyrogenic
Each mL contains 0.2 mg NICARDIPINE HYDROCHLORIDE in
8.3 mg SODIUM CHLORIDE, USP with 0.0384 mg CITRIC ACID
ANHYDROUS, USP and 3.84 mg SORBITOL, NF. HYDROCHLORIC ACID
and/or SODIUM HYDROXIDE may have been added to adjust pH.
DOSAGE: See package insert for complete information on dosage and
administration.
CAUTIONS: Check for minute leaks by squeezing bag firmly. If leaks are
found, discard bag as sterility may be impaired. Do not use unless solution
is clear. Do not add supplemental medication. Must not be used in series
connections.
STORAGE: 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
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Marketed by:
EKR Therapeutics, Inc.
Bedminster, NJ 07921 USA
Manufactured by:
Baxter Healthcare Corporation
Deerfield, IL 60015 USA
To report an adverse event, record the lot # and call 1-877-207-5802
PL 2501 Plastic
07-34-58-496
C08-35

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019734Orig1s014

CHEMISTRY REVIEW(S)

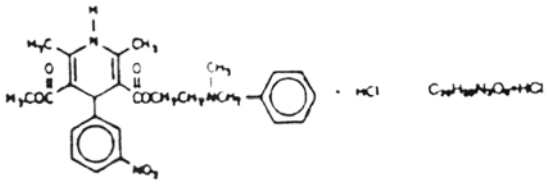
Division of Post Approval Marketing Evaluation IV
Chemist Review of Supplement

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 Therapuetics
   1545 US Highway Route 206
   Bedminster, NJ 07921

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

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 (b) (4) is referenced to DMF (b) (4) 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* (b) (4) *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.* (b) (4)

(b) (4) *. Furthermore, toxicology tests have shown no adverse effects in a30 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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/s/

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

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

CENTER FOR DRUG EVALUATION AND RESEARCH

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

Letter	Stamp	Review Request	Assigned to Reviewer
May 15, 2008	March 18, 2008	June 12, 2008	June 23, 2008

Submission History (for amendments only) – N/A

Applicant/Sponsor
Name: EKR Therapeutics, Inc.
Address: 545 US Highway Rt 206, Bedminister, NJ 07921
Representative: Alexander Mironov, Director, Regulatory Affairs
Telephone: 877-435-2524 ext. 123, or Nancy Teasdale (b) (6) (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 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: (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/SCF014 for addition of a new GALAXY (b) (4) 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 then 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 (b) (4) 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) (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 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

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/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)

CLINICAL PHARMACOLOGY REVIEW

NDA	19-734
NDA type	Supplement SCF-014: Prior Approval Supplement/Formulation Change Supplement
Submission Date	May 14, 2008
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 Hydrocholride
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 ((b) (4) 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

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_{last}, and AUC_{inf}.

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

Parameter (units)	N	Test (Pre-MixBag)/ Reference (Ampul)[a]	90% Confidence Interval[b]
Cmax (ng/ml)	26	0.999	(94 - 106)
AUClast (ng*hr/ml)	26	0.979	(92 - 103)
AUCinf (ng*hr/ml)	24	0.955	(92 - 100)

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

APPENDIX 4.1

Includes:

NDA 19-734/SCF-014

Proposed Labeling

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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.

Treatment Sequence	N [a]	Period 1	Washout	Period 2
A/B	Up to 15	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).	→	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).
B/A	Up to 15	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).	→	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).
		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-l0 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.

Study Drug	Dose Level and Frequency	Total No. Doses
Treatment A: Test Drug		
Cardene I.V. Double Strength Premixed Injection in 5% Dextrose	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).	1
Treatment B: Reference Drug		
Cardene I.V. approved ampule product	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).	1

Formula Components	Treatment A Cardene I.V. Double Strength (0.2 mg/mL) Premixed Injection Formulation	Treatment B Cardene I.V. Approved Ampule Product Diluted with D5W
Nicardipine hydrochloride (mg/mL)	0.20	0.10
Citric Acid (mg/mL)	(b) (4)	0.02
Sodium Hydroxide (mg/mL)	As needed to adjust pH	0.004
Citric or Hydrochloric Acid	As needed to adjust pH	As needed to adjust pH
Dextrose (mg/mL)	50	48
Sorbitol (mg/mL)	none	1.9
(b) (4)		

Abbreviations: D5W = 5% dextrose in water solution (b) (4)

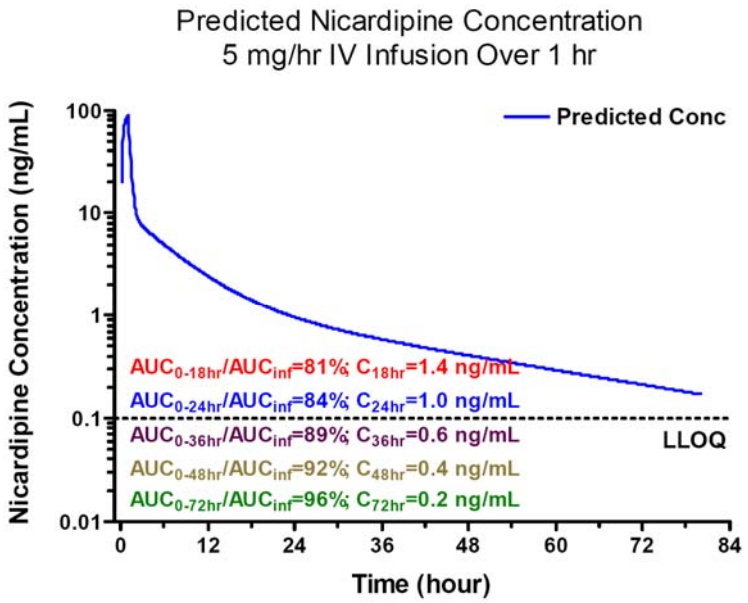
Selection of the Doses

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.



Nicardipine Drug Concentration Simulation

Simulation was performed using population typical values derived from the population PK modeling to fit data to support NDA 19-734

Data Evaluation:

- ***Analytical Method:*** Plasma concentrations of nicardipine hydrochloride were determined using a validated LC/MS/MS method previously validated under (b) (4) (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 $\log_e$-transformation, AUC_{0-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

PARAMETER	UNITS	TREATMENT			
		N	Pre-Mix Bag	N	Ampul
Cmax	(ng/ml)	28	58.8 (15.l)	27	59.0 (11.0)
AUClast	(ng*hr/ml)	28	107 (18.2)	27	109 (17.3)
AUCinf	(ng*hr/ml)	28	111 (19.5)	25	114 (17.5)
AUClast/AUCinf	-	28	0.960 (0.0267)	25	0.964 (0.0200)
λz	(1/hour)	28	0.0687 (0.0223)	25	0.0685 (0.0160)

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

Parameter (units)	N	Test (Pre-MixBag)/ Reference (Ampul)[a]	90% Confidence Interval[b]
Cmax (ng/ml)	26	99.9	(94 - 106)
AUClast (ng*hr/ml)	26	97.9	(92 - 103)
AUCinf (ng*hr/ml)	24	95.5	(92 - 100)

a. Ratio of geometric means of the parameter for the two treatments (expressed as a percent). Natural log transformed ratios transformed back to linear scale.
b. 90% confidence interval for ratio of geometric means of the two treatment groups (expressed as a percent). Natural log transformed confidence limits transformed back to linear scale.

Abbreviations:
λz = apparent terminal phase elimination rate constant;
AUCinf = AUC extrapolated to infinity;
AUClast = area under the concentration curve assessed to the last measured concentration;
Cmax = maximum plasma drug concentration;
N = number of subjects; SD = standard deviation.

The 90% confidence intervals for the comparison of total racemic nicardipine Cmax, AUClast, and AUCinf 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. (b) (6) was withdrawn at Period 2 Check-in for abnormal laboratory values (3 clinically significant hepatic values). Subject No. (b) (6) was withdrawn during dosing on Period 1, Day I, for moderate, related AEs of tachycardia and anxiety. Subject No. (b) (6) 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.*

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/s/

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

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019734Orig1s014

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: DMETS
Mail: ODS

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

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
September 22, 2008		19-734		

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Nicardipine Hydrochloride		Calcium Channel Blocker	October 14, 2008

NAME OF FIRM: EKR

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
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY 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 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
- ☐ 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	METHOD OF DELIVERY (Check one)
Lori Wachter	X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

8 Page(s) have been Withheld in Full as Draft Labeling immediately following this page.

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/s/

Lori Wachter
9/23/2008 11:02:48 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

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	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
June 12, 2008		19-734	SCF-014	May 15, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Cardene			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
- ☐ BIOAVAILABILTY 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	METHOD OF DELIVERY (Check one)
Teshara G. Bouie	☒ DFS ☐ EMAIL ☐ MAIL ☒ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Teshara Bouie
6/12/2008 04:49:32 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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