DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 019734/S-017

SUPPLEMENT APPROVAL

EKR Therapeutics
Attention: George Wagner
Vice President, Regulatory Affairs
1545 US Highway 206
Third Floor
Bedminster, NJ 07921

Dear Mr. Wagner:

Please refer to your Supplemental New Drug Application (sNDA) dated September 30, 2010, received October 1, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Cardene (nicardipine hydrochloride) 0.1 mg, 0.2 mg Premixed Solution, and 25 mg/10mL Ampules for Intravenous administration.

This "Prior Approval" supplemental new drug application provides for changes to the **HIGHLIGHTS**, **CONTRAINDICATIONS,** and **DRUG INTERACTIONS** section of the Cardene Premixed package insert and the **CLINICAL PHARMACOLOGY**, **CONTRAINDICATIONS**, **WARNINGS**, **PRECAUTIONS**, **CARCINOGENICITY**, **MUTAGENICITY**, **IMPAIRMENT OF FERTILITY**, **ADVERSE EXPERIENCES,** and **DOSAGE AND ADMINISTRATION** sections of the Cardene 25 mg/mL Ampules package insert.

The following changes were made:

The following changes were made in the Cardene 0.1 mg/mL and 0.2 mg/mL Premixed Injection labels:

1. The cross references were updated throughout the label to reflect deleted sections of the text.

2. Under **HIGHLIGHTS/DOSAGE AND ADMINSTRATION**, the sections were reordered to read:

   2. Dosage and administration
   2.1 Recommended Dosing
   2.2 Monitoring
   2.3 Instructions for Administration

3. Under **WARNINGS AND PRECAUTIONS/Use in Patients with Impaired Renal Function,** the word "carefully" was replaced by the word "gradually" in the last sentence of the first paragraph. The sentence now reads:

   Titrate gradually in patients with renal impairment.

4. Under **DRUG INTERACTIONS/Cimetidine,** the language in the second sentence of the first paragraph was changed from the passive voice to the active voice. The sentence now reads:
   Frequently monitor response in patients receiving both drugs.

5. Under **USE IN SPECIFIC POPULATIONS/Pregnancy**, in the third sentence in the fifth paragraph, the letters "RH" replaced the letters "HR." The sentence now reads:

   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).

6. The revision date and version number were updated.

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

The following changes were made in the Cardene Ampule label:

1. Under **CLINICAL PHARMACOLOGY/Hepatic Function**, the first sentence was changed from:

   Because nicardipine is metabolized by the liver, plasma concentrations are influenced by changes in hepatic function.

   To:

   Because the liver extensively metabolizes nicardipine, plasma concentrations are influenced by changes in hepatic function.

2. Under **INDICATIONS AND USAGE**, the language in the second sentence in the first paragraph was changed from passive voice to active voice. The sentence now reads:

   For prolonged control of blood pressure, transfer patients to oral medication as soon as their clinical condition permits (see "Dosage and Administration").

3. Under **CONTRAINDICATIONS**, the first sentence was deleted. The paragraph now reads:

   Cardene® I.V. is 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.

4. Under **WARNINGS**, the following sections were deleted:

   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 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.

5. Under **WARNINGS/Use in Patients with Congestive Heart Failure,** the section was 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., particularly in combination with a beta-blocker, in patients with heart failure or significant left ventricular dysfunction because of possible negative inotropic effects.

6. Under **WARNINGS/Peripheral Vein Infusion Site,** the section was changed from:

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.

To:

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

7. Under **PRECAUTIONS**/**General**, the section was 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.

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.

To:

Blood Pressure: 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.

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.

Use in Patients with Impaired Renal Function: When Cardene I.V. was given to mild to moderate hypertensive patients with moderate renal impairment, a significantly lower systemic clearance and higher area under the curve (AUC) was observed. These results are consistent with those seen after oral administration of nicardipine. Titrate gradually in patients with renal impairment.

8. Under **PRECAUTIONS /Drug Interactions**, the following text was deleted:

   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.

9. Under **PRECAUTIONS /Drug Interactions**, the first paragraph was changed from:

   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**").

   To:

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

10. Under **PRECAUTIONS /Drug Interactions**, the second paragraph was changed from:

    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.

To:

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

11. Under **PRECAUTIONS /Drug Interactions**, the following text was deleted:

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.

12. Under **PRECAUTIONS /Drug Interactions**, the first paragraph was changed from:

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.

To:

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

13. Under **PRECAUTIONS/Carcinogenesis, Mutagenesis, Impairment of Fertility**, the last sentence in the first paragraph was changed from:

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).

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).

14. Under **PRECAUTIONS/Carcinogenesis, Mutagenesis, Impairment of Fertility**, the second paragraph was 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 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.

To:

Pregnancy Category C
There are no adequate and well-controlled studies of nicardipine use in pregnant women. However, limited human data in pregnant women with preeclampsia or pre-term labor are available. In animal studies, no embryotoxicity occurred in rats with oral doses 8 times the maximum recommended human dose (MRHD) based on body surface area (mg/m2), but did occur in rabbits with oral doses at 24 times the maximum recommended human dose (MRHD) based on body surface area (mg/m2). 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/m2) (5 mg/kg/day) (rats) and 0.03 times the MRHD based on body surface area (mg/m2) (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/m2) (10 mg/kg/day) in rats and at 0.05 times the MRHD based on body surface are (mg/m2) (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/m2) (50 and 150 mg/kg/day). Embryotoxicity occurred at the high dose along with signs of maternal toxicity (marketed maternal weight gain suppression). New Zealand albino

rabbits received oral nicardipine during organogenesis, at doses up to 16 times the MHRD based on body surface area (mg/m2) (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/m2) (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.

15. Under **PRECAUTIONS**/**Nursing Mothers**, the first paragraph was 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.

16. Under **PRECAUTIONS**/**Geriatric Use,** the section was changed from:

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

To:

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

Clinical studies of nicardipine did not include sufficient numbers of subjects aged 65 and

over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, use low initial doses in elderly patients, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

17. Under **ADVERSE EXPERIENCES,** the following text was 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.

18. Under **ADVERSE EXPERIENCES**, the table was revised to read:

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

Adverse Event	**Cardene I.V. (n=144)**	**Placebo (n=100)**
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)

19. Under **ADVERSE EXPERIENCES**, the following text was deleted under the Table of adverse events:

    RARE EVENTS

20. Under **ADVERSE EXPERIENCES**, the text found under the Table of Adverse Events was changed from:

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

    To:

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

21. Under **OVERDOSAGE**, the third paragraph was changed from:

    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.

To:

For treatment of overdosage, implement standard measures including monitoring of cardiac and respiratory functions. Position the patient so as to avoid cerebral anoxia. Use vasopressors for patients exhibiting profound hypotension.

22. Under **DOSAGE AND ADMINISTRATION**, the first paragraph was changed from:

Cardene® I.V. (nicardipine hydrochloride) 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 dose to achieve the desired blood pressure reduction. Individualize dosage depending on the blood pressure to be obtained and the response of the patient.

23. Under **DOSAGE AND ADMINISTRATION**, the following text was added:

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

24. Under **Dosage**, the first sentence of the first paragraph was changed from:

As a Substitute for Oral Nicardipine Therapy

To:

Dosage as a Substitute for Oral Nicardipine Therapy

25. Under **Dosage**, the table was revised as follows:

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

26. Under **Dosage**, the second paragraph was 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).

27. Under **Dosage**, the following text was deleted:

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**").

28. Under **TRANSFER TO ORAL ANTIHYPERTENSIVE AGENTS**, the section was 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 Transfer to Oral Antihypertensive Agents
    Discontinuation of infusion is followed by a 50% offset 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.

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

29. The words “nicardipine capsules” were changed to “oral nicardipine” throughout the label.

30. There were several editorial changes made throughout the label (i.e. Headings bolded and replaced with all caps, the word “are” changed to “area”, the word “marketed” changed to “marked”, the word “gesation” changed to “gestation”)

31. The revision date and version number were updated.

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

We have completed our review of this supplemental 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, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to 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, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

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:
Content of Labeling

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
02/07/2011