CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022276Orig1s008

Trade Name:	NICARDIPINE HYDROCHLORIDE
Generic or Proper Name:	nicardipine hydrochloride
Sponsor:	EXCELA Pharma Sciences LLC
Approval Date:	April 07, 2016
Indication:	Nicardipine hydrochloride injection is a calcium channel blocker indicated for the short-term treatment of hypertension when oral therapy is not feasible.

CENTER FOR DRUG EVALUATION AND RESEARCH

022276Orig1s008

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22276/S-008

SUPPLEMENT APPROVAL

Exela Pharma Sciences, LLC.
Attention: Jonathan E. Sterling
Vice President of Quality and Regulatory Affairs
P.O. Box 818
1245 Blowing Rock Blvd.
Lenoir, NC 28645

Dear Mr. Sterling:

Please refer to your Supplemental New Drug Application (sNDA) dated March 27, 2013, received March 29, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nicardipine Hydrochloride Injectable 0.1mg/mL and 0.2 mg/mL.

We acknowledge receipt of your amendment dated December 04, 2015 which constituted a complete response to our July 25, 2013 action letter, and your amendment dated April 04, 2016 which provided updated labeling.

This supplemental new drug application proposes new premixed formulations; Nicardipine Hydrochloride Premixed Injection, 0.1mg/mL and 0.2mg/mL, in 0.9% Sodium Chloride.

APPROVAL & LABELING

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

We have the following additional comment:

PRODUCT QUALITY MICROBIOLOGY

It is acknowledged that the endotoxin limit listed in the release specification for Nicardipine Hydrochloride Premixed Injection has been lowered to NMT (b) (4) EU/mg; however the endotoxin limit in the drug product stability specification was not lowered and remains at (b) (4) EU/mg. The stability endotoxin limit should be lowered to NM (b) (4) EU/mg.

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 that includes labeling changes 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).

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your December 04, 2015 submission containing final printed carton and container labels.

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 contact Sabry Soukehal, Regulatory Health Project Manager, at (240) 402-6187.

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(S):
Agreed upon labeling text
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 L STOCKBRIDGE
04/07/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022276Orig1s008

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022276/S-008

COMPLETE RESPONSE

Exela Pharma Sciences, LLC
Attention: Jonathan Sterling
Vice President of Quality, Regulatory and Product
1325 William White Place
PO Box 818
Lenoir, NC 28645

Dear Mr. Sterling:

Please refer to your Supplemental New Drug Application (sNDA) dated March 27, 2013, received March 29, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nicardipine Hydrochloride 0.1 mg/mL and 0.2 mg/mL injection.

We acknowledge receipt of your amendments dated June 4, 14, July 10 and 11, 2013.

This supplemental new drug application proposes new premixed formulations, Nicardipine Hydrochloride Premixed Injection, 0.1 mg/mL and 0.2 mg/mL, in 0.9% sodium chloride.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. Based on the data provided in the supplement and the July 2, 2013 summary tables, please clarify for the following:

   a) Impurity specification for [redacted] (Impurity [redacted] as NMT [redacted]% is not supported by release and stability data provided. The approved limit for Impurity [redacted] is NMT [redacted]%. Provide data to justify increasing the limit from NMT [redacted]% to NMT [redacted]% based on data.

   b) Similarly [redacted] (Impurity [redacted] shows out of specifications (OOS) results at 6 month time point at accelerated conditions of 40 ºC. However, this impurity [redacted] is within limits at the intermediate condition of 30 ºC. Provide additional long-term and intermediate condition (30 ºC) stability data to support the shelf-life of the product since Impurity [redacted] is OOS at 40 ºC conditions.

   c) Justify the specification of NMT [redacted]% for [redacted] which is a new specification proposed for these [redacted] oposed strengths in the new flexibags. The

limits are not supported by stability data which shows levels NMT (b) (4) % even at accelerated conditions.

d) An impurity listed as (b) (4) with a proposed specification of (b) (4) (b) (4) is monitored during stability studies of the drug product. This impurity is not listed as part of the proposed release and stability specifications. Please provide details on this impurity and propose specifications related to this impurity in the drug product release and stability specifications based on data.

2. Your application referenced the Drug Master File (DMF) (b) (4) This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder on July 24, 2013. These deficiencies must be adequately addressed before this application can be approved. As part of your response to this letter, include the date the DMF holder amended their DMF to address the deficiencies.

3. There is a discrepancy in the information submitted in this supplement and that provided in your July 2, 2013 response via email regarding the manufacturing and controls sites for the proposed strengths. Provide a list of all manufacturing and controls (release as well as stability testing) sites to be used for manufacture and control of the proposed strengths and their responsibilities. Include appropriate information such as FEI #, address, contact person, phone number, etc.

4. Based on the data provided in Section 32p7 for container closure extractable and leachables, please provide data that show the amount of extractables and leachables are at a safe limit.

REGULATORY

5. Under 21 CFR 314.54(a)(1)(vi), a 505(b)(2) application must contain a patent certification or statement with respect to any relevant patents that claim the listed drug and that claim any other drugs on which the investigations relied on for approval of the application were conducted, or that claim a use for the listed or other drug. Your 505(b)(2) application relies upon the Agency's finding of safety and effectiveness for NDA 19734 for Cardene (nicardipine hydrochloride) injection and I.V., for which you submitted Paragraph IV certification with respect to U.S. Patent Numbers 7,612,102 ('102 patent), 7,659,291 ('291 patent), and 8,455,524 ('524 patent) listed in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book) as described in 21 CFR 314.54(a)(1)(vi)). However, you have not provided documentation of receipt by each person identified in 21 CFR 314.52(a) of the required notice of Paragraph IV certification for the '524 patent. Acceptable forms of documentation are described in 21 CFR 314.52(e).

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

1. In your response dated July 2, 2013, you stated that the stability studies were conducted using the proposed commercial container closure. However, when requested a sample of the bag used on June 26, 2013, you stated that the bags were not yet manufactured. Please clarify this discrepancy and provide a sample of the bag.

2. Your application states that [redacted] include a [redacted] Clarify the [redacted] drug product [redacted]

3. [redacted]

4. Your drug product release specifications call for an endotoxin limit of [redacted] EU/mg, while your stability specifications call for an endotoxin limit of [redacted] EU/mg. Provide a justification for this difference in endotoxin specifications.

5. When administered at the highest level recommended in proposed labeling, the maximum specification for endotoxin levels (release specification of [redacted] EU/mg) would result in a patient exposure higher than what is recommended in USP <85> [redacted] kg hour.) While this endotoxin specification was previously approved for the drug product, you should revise this specification to ensure that the recommended exposure is not exceeded.

LABELING

1. Please submit draft labeling revised as follows.
   a. Revise the statement [redacted] found throughout the insert labeling with the USP recognized terminology of "0.9% Sodium Chloride Injection".
   b. Delete the [redacted]" reference as an expression for the infusion rate (in the Dosage and Administration section 2.4 Dosage for Initiation of Therapy in a Drug-Free Patient, Subsection Titration) and only present the infusion rate referencing the "mg/hr" for the total amount of drug intended per hour. The "[redacted]" will be dependent upon the concentration selected and there are two concentrations being proposed for this supplement.
   c. Under the Dosage Forms and Strengths section 3 of the insert labeling, we recommend revising the strength statement from "20 mg (0.1 mg/mL)" and "40 mg (0.2 mg/mL)" to read "20 mg in 200 mL (0.1 mg/mL)" and "40 mg in 200 mL (0.2 mg/mL)", respectively.
   d. Similarly, under the How Supplied/Storage and Handling section 16.1 of the insert labeling, we recommend revising the strength statement from "0.1 mg/mL in 200 mL…" and "0.2 mg/mL in 200 mL…" to read "20 mg in 200 mL (0.1 mg/mL)" and "40 mg in 200 mL (0.2 mg/mL)", respectively.

Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. 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 include annotations with the supplement number for previously-approved labeling changes.

2. Please submit draft carton and container labeling revised as follows:

Bag (inner) Label

a. Consider increasing the differentiation between the two strengths by using a different color scheme for one of the strengths (e.g., blue color for the 0.1 mg/mL strength). The blue color would help differentiate the lower strength (0.1 mg/mL) from the black color used on the label for the higher strength (0.2 mg/mL).

b. Revise the statement [redacted] (b) (4) found under the product name with the USP recognized terminology of "0.9% Sodium Chloride Injection".

c. The route of administration is absent. Therefore, we recommend adding the route of administration statement "For Intravenous Infusion".

d. Below the statement, "Single Dose Container", add the statement "Discard Unused Portion" to reinforce to the user that the contents of the bag should be discarded after retrieving the required dose.

e. Increase the font size of the strength expressions (e.g., 20 mg in 200 mL and 0.1 mg/mL), and revise the strength statements to appear in a stacked format. For example:

20 mg in 200 mL
(0.1 mg/mL)

f. Revise the established name such that it includes mixed case letters (e.g., "Nicardipine Hydrochloride").

g. Ensure the lot and expiration date is present on the label as it appears to be missing.

h. Minimize the prominence of the distributor name, West-Ward, to avoid competing with other important information on this crowded label.

Overwrap Labeling

i. See 5a through 5h above.

ii. If possible, increase the overall size of the label to improve readability of all the information presented on the labeling.

iii. Remove the [redacted] and avoid the use of the [redacted] for the lower strength of 20 mg in 200 mL (0.1 mg/mL) to reduce potential for confusion with the same proposed [redacted] scheme on the 40 mg in 200 mL (0.2 mg/mL). In addition, we note the removal of the [redacted] scheme may further help differentiate the proposed (0.1 mg/mL) strength [redacted]

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants", May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
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/

NORMAN L STOCKBRIDGE
07/25/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022276Orig1s008

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NICARDIPINE HYDROCHLORIDE safely and effectively. See full prescribing information for NICARDIPINE HYDROCHLORIDE.

NICARDIPINE HYDROCHLORIDE injection, for intravenous use
Initial U.S. Approval: 1988

----------RECENT MAJOR CHANGES----------
Dosage and Administration (2.2) 04/2016

---------- INDICATIONS AND USAGE----------
Nicardipine hydrochloride injection is a calcium channel blocker indicated for the short-term treatment of hypertension when oral therapy is not feasible.

----------DOSAGE AND ADMINISTRATION----------
- Individualize dosage based upon the severity of hypertension and response of the patient during dosing (2.1).
- Single dose vials must be diluted before use (2.2).
- When substituting for oral nicardipine therapy, use the intravenous infusion rate as follows (2.3):

Oral Nicardipine Dose	Equivalent IV Infusion Rate
20 mg q8h	0.5 mg/hr
30 mg q8h	1.2 mg/hr
40 mg q8h	2.2 mg/hr

- In a drug-free patient, initiate therapy at 5 mg/hr. Increase the infusion rate by 2.5 mg/hr to a maximum of 15 mg/hr until desired blood pressure reduction is achieved. For a gradual blood pressure reduction the rate can be increased every 15 minutes, for a rapid reduction, every 5 minutes (2.4).
- If hypotension or tachycardia ensues, discontinue the infusion. After stabilized, patient can be restarted at low doses such as 3 to 5 mg/hr (2.5).

---------- DOSAGE FORMS AND STRENGTHS----------
- 25 mg/10 ml (2.5 mg/mL) single-dose vial (3)
- 20 mg in 200 ml (0.1 mg/mL) flexible container (3)
- 40 mg in 200 ml (0.2 mg/mL) flexible container (3)

---------- CONTRAINDICATIONS ----------
- Do not use in patients with advanced aortic stenosis (4.1).

---------- WARNINGS AND PRECAUTIONS----------
- To reduce the possibility of venous thrombosis, phlebitis, and vascular impairment, do not use small veins, such as those on the dorsum of the hand or wrist. Avoid intraarterial administration or extravasation (5.7).
- To minimize the risk of peripheral venous irritation, change the site of infusion of nicardipine every 12 hours (5.7).
- Nicardipine is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal. Withdraw beta-blockers gradually (5.8).
- Closely monitor response in patients with angina (5.3), congestive heart failure (5.4), impaired hepatic function (5.5), portal hypertension (5.5), and renal impairment (5.6) and pheochromocytoma (5.9).

---------- ADVERSE REACTIONS----------
Most common adverse reactions are headache (13%), hypotension (5%), tachycardia (4%) and nausea/vomiting (4%).
To report SUSPECTED ADVERSE REACTIONS, contact West-ward Pharmaceuticals at 1-877-233-2001 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------
- Cimetidine increases nicardipine plasma levels (7.3).
- Nicardipine increases cyclosporine plasma levels. Monitor cyclosporine levels when co-administering with nicardipine (7.5).

---------- USE IN SPECIFIC POPULATIONS ----------
- Pregnancy: Based on animal data, may cause fetal harm (8.1).
- Nursing Mothers: It is recommended that women who wish to breastfeed should not be given this drug (8.3).
- Safety and efficacy in patients under the age of 18 have not been established (8.4).

Revised: 04/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE

1.1 Hypertension

Nicardipine hydrochloride injection is indicated for the short-term treatment of hypertension when oral therapy is not feasible or desirable. For prolonged control of blood pressure, transfer patients to oral medication as soon as their clinical condition permits *[see Dosage and Administration (2.6)]*.

2 DOSAGE AND ADMINISTRATION

2.1 General Information

Individualize dosing based on the severity of hypertension and the response of the patient during dosing. Monitor blood pressure and heart rate both during and after the infusion to avoid tachycardia or too rapid or excessive reduction in either systolic or diastolic blood pressure.

Administer Nicardipine Hydrochloride by slow continuous infusion by a central line or through a large peripheral vein. Change the infusion site every 12 hours if administered via peripheral vein *[see Intravenous Infusion Site (5.7)]*.

2.2 Inspection and Preparation

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Single Dose Vials

Dilution
Single dose vials must be diluted before infusion.

Each vial (25 mg) must be diluted with 240 mL of compatible intravenous fluid (see below), resulting in 250 mL of solution at a concentration of 0.1 mg/mL.

Compatibility
Nicardipine hydrochloride injection has been found compatible and stable in polyvinyl chloride containers for 24 hours at controlled room temperature with:

Dextrose (5%) Injection, USP
Dextrose (5%) and Sodium Chloride (0.45%) Injection, USP
Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP
Dextrose (5%) with 40 mEq Potassium, USP
Sodium Chloride (0.45%) Injection, USP
Sodium Chloride (0.9%) Injection, USP

Nicardipine hydrochloride is not compatible with Sodium Bicarbonate (5%) Injection, USP or Lactated Ringer's Injection, USP.

Flexible Containers

Dilution is not required for Nicardipine Hydrochloride in 0.9% Sodium Chloride Injection.

Check the container for minute leaks prior to use by squeezing the bag firmly; ensure that the seal is intact. If leaks are found, discard solution as sterility may be impaired.

Do not combine Nicardipine Hydrochloride in 0.9% Sodium Chloride Injection with any product in the same intravenous line or premixed container. Do not add supplementary medication to the bag. Protect from light until ready to use.

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

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

2.3 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 Nicardipine Dose	Equivalent Intravenous Infusion Rate
20 mg q8h	0.5 mg/hr
30 mg q8h	1.2 mg/hr
40 mg q8h	2.2 mg/hr

2.4 Dosage 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. Nicardipine hydrochloride injection 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.

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

Titration

For a gradual reduction in blood pressure, initiate therapy at a rate of 5 mg/hr. If desired blood pressure reduction is not achieved at this dose, increase the infusion rate by 2.5 mg/hr every 15 minutes up to a maximum of 15 mg/hr, until desired blood pressure reduction is achieved. For more rapid blood pressure reduction, titrate every 5 minutes.

Maintenance

Adjust the rate of infusion as needed to maintain desired response.

2.5 Conditions Requiring Infusion Adjustment

Hypotension or Tachycardia: In case of hypotension or tachycardia, discontinue infusion. When blood pressure and heart rate stabilize, restart infusion at low doses such as 30 mL/hr to 50 mL/hr (3 mg/hr to 5 mg/hr) and titrate to maintain desired blood pressure.

Infusion Site Changes: Change infusion site every 12 hours if administered via peripheral vein.

Impaired Cardiac, Hepatic, or Renal Function: Monitor closely when titrating nicardipine hydrochloride injection in patients with congestive heart failure or impaired hepatic or renal function *[see Warnings and Precautions (5.4, 5.5 and 5.6)]*.

2.6 Transfer to Oral Antihypertensive Agents

If treatment includes transfer to an oral antihypertensive agent other than nicardipine capsules, initiate oral therapy upon discontinuation of nicardipine hydrochloride injection.

When switching to a TID regimen of nicardipine capsules, administer the first dose 1 hour prior to discontinuation of the infusion.

3 DOSAGE FORMS AND STRENGTHS

Nicardipine hydrochloride is available in the following presentations:

- 25 mg nicardipine hydrochloride in 10 mL injection (2.5 mg/mL) in a single dose vial
- 20 mg nicardipine hydrochloride in 200 mL 0.9% sodium chloride injection (0.1 mg/mL) in a flexible container
- 40 mg nicardipine hydrochloride in 200 mL 0.9% sodium chloride injection (0.2 mg/mL) in a flexible container

4 CONTRAINDICATIONS

4.1 Advanced Aortic Stenosis

Do not use nicardipine in patients with advanced aortic stenosis because of the afterload reduction effect of nicardipine. Reduction of diastolic pressure in these patients may worsen rather than improve myocardial oxygen balance.

5 WARNINGS AND PRECAUTIONS

5.1 Excessive Pharmacologic Effects

In administrating nicardipine, close monitoring of blood pressure and heart rate is required. Nicardipine may occasionally produce symptomatic hypotension or tachycardia. Avoid systemic hypotension when administering the drug to patients who have sustained an acute cerebral infarction or hemorrhage.

5.2 Rapid Decreases in Blood Pressure

No clinical events have been reported suggestive of a too rapid decrease in blood pressure with nicardipine. 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.

5.3 Use in Patients with Angina

Increases in frequency, duration, or severity of angina have been seen in chronic oral therapy with nicardipine capsules. Induction or exacerbation of angina has been seen in less than 1% of coronary artery disease patients treated with nicardipine. The mechanism of this effect has not been established.

5.4 Use in Patients with Congestive Heart Failure

Nicardipine 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, monitor vital signs carefully when using nicardipine, particularly in combination with a beta-blocker, in patients with CHF or significant left ventricular dysfunction.

5.5 Use in Patients with Impaired Hepatic Function

Since nicardipine is metabolized in the liver, consider lower dosages and closely monitor response. Nicardipine administered intravenously increased hepatic venous pressure gradient by 4 mmHg in cirrhotic patients at high doses (5 mg/20 min) in one study. Use caution in patients with portal hypertension.

5.6 Use in Patients with Impaired Renal Function

When nicardipine 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 patients with more than mild renal impairment.

5.7 Intravenous Infusion Site

To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, extravasation, and the rare 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, consider changing the site of the drug infusion every 12 hours.

5.8 Beta-Blocker Withdrawal

Nicardipine is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal. Withdraw beta-blockers gradually.

5.9 Use in Patients with Pheochromocytoma

Only limited clinical experience exists in use of nicardipine for patients with hypertension from pheochromocytoma.

6 ADVERSE REACTIONS

6.1 Adverse Reactions Observed in Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Two hundred forty-four patients participated in two multicenter, double-blind, placebo-controlled trials of nicardipine. Adverse experiences were generally not serious and most were expected consequences of vasodilation. Adverse reactions occasionally required dosage adjustment. Therapy was discontinued in approximately 12% of patients, mainly due to hypotension, headache, and tachycardia. Adverse reactions that occurred more often on nicardipine than on placebo by at least 2% were headache (13%) and nausea/vomiting (4%).

The following adverse reactions have been reported in clinical trials or in the literature during the use of intravenously administered nicardipine.

Body as a Whole: fever, neck pain
Cardiovascular: angina pectoris, atrioventricular block, ST segment depression, inverted T wave, deep-vein thrombophlebitis
Digestive: dyspepsia
Hemic and Lymphatic: thrombocytopenia
Metabolic and Nutritional: hypophosphatemia, peripheral edema
Nervous: confusion, hypertonia
Respiratory: respiratory disorder
Special Senses: conjunctivitis, ear disorder, tinnitus
Urogenital: urinary frequency

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

7 DRUG INTERACTIONS

7.1 Antihypertensive Agents

Since nicardipine hydrochloride injection 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 to treat promptly any undesired effects from concomitant administration.

7.2 Beta-Blockers

In most patients, nicardipine hydrochloride injection can safely be used concomitantly with beta-blockers. However, monitor response carefully when combining nicardipine hydrochloride injection with a beta-blocker in the treatment of congestive heart failure patients *[see Warnings and Precautions (5.4)]*.

7.3 Cimetidine

Cimetidine has been shown to increase nicardipine plasma concentrations with oral nicardipine administration. Carefully monitor patients receiving the two drugs concomitantly. Data with other histamine-2 antagonists are not available.

7.4 Digoxin

Studies have shown that oral nicardipine usually does not alter digoxin plasma concentrations.

7.5 Cyclosporine

Concomitant administration of oral nicardipine and cyclosporine results in elevated plasma cyclosporine levels. Monitor closely plasma concentrations of cyclosporine during nicardipine hydrochloride injection administration, and adjust the dose of cyclosporine accordingly.

7.6 *In Vitro* Interaction

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies of nicardipine use in pregnant women. There are limited human data in pregnant women with pre-eclampsia and preterm labor. In animal reproduction and developmental toxicity studies, evidence of fetal harm was observed. Therefore use nicardipine during pregnancy only if the potential benefit justifies the potential risk to the fetus.
In reproduction studies conducted in rats and rabbits, increased embryolethality occurred when nicardipine was administered intravenously at doses equivalent to human intravenous doses of 1.6 (rats) and 0.32 mg/kg/day (rabbits).

Increased embryolethality was also observed when nicardipine was administered orally to pregnant rabbits at a dose equivalent to a human oral dose of about 48 mg/kg/day (a dose 24 times the maximum recommended human oral dose and one associated with marked maternal body weight gain suppression). At a lower oral dose, equivalent to a human dose of about 32 mg/kg/day (16 times the maximum recommended human oral dose), in a different strain of rabbit, there were no adverse effects on the fetus, though there was increased maternal mortality. There was no evidence of embyolethality or teratogenicity when pregnant rats were administered nicardipine orally at a dose equivalent to a human oral dose of about 16 mg/kg/day (8 times the MRHD); however, dystocia, reduced birth weight, reduced neonatal survival and reduced neonatal weight gain were reported *[see Nonclinical Toxicology (13.3)]*.

8.3 Nursing Mothers

Nicardipine is minimally excreted into human milk. Among 18 infants exposed to nicardipine through breast milk in the postpartum period, calculated daily infant dose was less than 0.3 mcg and there were no adverse events observed. It is recommended that women who wish to breastfeed should not be given this drug.

In a study of 11 women who received oral nicardipine 4 days to 14 days postpartum, 4 women received immediate-release nicardipine 40 to 80 mg daily, 6 women received sustained-release nicardipine 100 mg to 150 mg daily, and one woman received intravenous nicardipine 120 mg daily. The peak milk concentration was 7.3 mcg/L (range 1.9 to 18.8), and the mean milk concentration was 4.4 mcg/L (range 1.3 to 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 (less than 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 less than 0.3 mcg daily or 0.015% to 0.004% of the therapeutic dose in a 1 kg infant.

8.4 Pediatric Use

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

8.5 Geriatric Use

The steady-state pharmacokinetics of nicardipine are similar in elderly hypertensive patients (greater than 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 concomitant disease of other drug therapy.

10 OVERDOSAGE

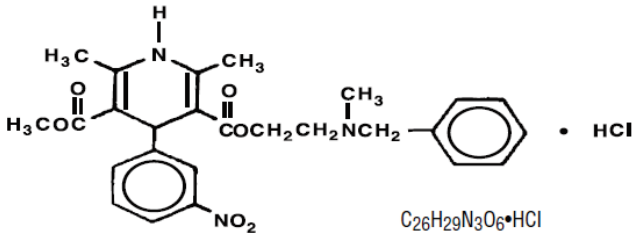
Several overdosages with orally administered nicardipine have been reported. One adult patient allegedly ingested 600 mg of nicardipine immediate release capsules, and another patient, 2160 mg of the sustained release formulation of nicardipine. Symptoms included marked hypotension, bradycardia, palpitations, 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 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.

11 DESCRIPTION

Nicardipine hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium channel blocker). Nicardipine hydrochloride for intravenous administration contains 2.5 mg/mL of nicardipine hydrochloride. 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 yellow to pale yellow, odorless, crystalline powder that has a melting point range of 165-170◦ C. It is soluble in methanol, sparingly soluble in ethanol, slightly soluble in acetone, chloroform and water. It has a molecular weight of 515.99.

Nicardipine hydrochloride injection is available as a sterile, non-pyrogenic, clear, yellow solution in 10 mL vials for intravenous infusion after dilution. Each mL contains 2.5 mg nicardipine hydrochloride, 0.305 mg benzoic acid, USP and 7.5 mg sodium chloride, USP, in Water for Injection, USP. Sodium hydroxide, NF, may have been added to adjust pH to 3.5.
Nicardipine Hydrochloride in 0.9% Sodium Chloride Injection is available as a single-use, ready-to-use, iso-osmotic, clear, yellow solution for intravenous administration in a 200 mL flexible container. Each mL contains 0.1 mg or 0.2 mg nicardipine hydrochloride in 9 mg Sodium Chloride, USP. Hydrochloric acid may have been added to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nicardipine inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle without changing serum calcium concentrations. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. The effects of nicardipine are more selective to vascular smooth muscle than cardiac muscle. In animal models, nicardipine produced relaxation of coronary vascular smooth muscle at drug levels which cause little or no negative inotropic effect.

12.2 Pharmacodynamics

Hemodynamics
Nicardipine produces significant decreases in systemic vascular resistance. In a study of intra-arterially administered nicardipine, the degree of vasodilation and the resultant decrease in blood pressure were more prominent in hypertensive patients than in normotensive volunteers. Administration of nicardipine to normotensive volunteers at dosages of 0.25 to 3 mg/hr for eight hours produced changes of less than 5 mmHg in systolic blood pressure and less than 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 nicardipine increases blood flow. Coronary dilatation induced by nicardipine 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, nicardipine, administered after beta-blockade, significantly improved systolic and diastolic left ventricular function.

In congestive heart failure patients with impaired left ventricular function, nicardipine 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 nicardipine (Coronary steal is the detrimental redistribution of coronary blood flow in patients with coronary artery disease from underperfused areas toward better perfused areas.) Nicardipine 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 nicardipine 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, nicardipine 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. Nicardipine 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 nicardipine. 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 nicardipine capsules in patients with severe liver disease, plasma concentrations were elevated and the half-life was prolonged *[see Warnings and Precautions (5.5)]*. Similar results were obtained in patients with hepatic disease when nicardipine hydrochloride was administered for 24 hours at 0.6 mg/hr.

Renal Function
When nicardipine 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) were 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 nicardipine capsules (20 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 was a transient increase in electrolyte excretion, including sodium *[see Warnings and Precautions (5.6)]*.

Acute bolus administration of nicardipine hydrochloride injection (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, nicardipine hydrochloride injection (10 mg over 20 minutes) increased GFR with no change in RPF when compared with placebo. In hypertensive type ll diabetic patients with nephropathy, nicardipine 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 nicardipine capsules, no evidence of increased bronchospasm was seen. In one of the studies, nicardipine capsules improved forced expiratory volume 1 second (FEV_1) and forced vital capacity (FVC) in comparison with metoprolol. Adverse reactions reported in a limited number of patients with asthma, reactive airway disease, or obstructive airway disease were similar to reactions in other patients treated with nicardipine capsules.

12.3 Pharmacokinetics

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

Following infusion, nicardipine plasma concentrations decline triexponentially, with a rapid early distribution phase (α-half-life of 3 minutes), an intermediate phase (ß-half-life of 45 minutes), and a slow terminal phase (y-half-life of 14 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 (Vd) using a non-compartment

model is 8.3 L/kg. The pharmacokinetics of nicardipine is linear over the dosage range of 0.5 mg/hr to 40 mg/hr.

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Rats treated with nicardipine in the diet (at concentrations calculated to provide daily dosage levels of 5, 15, or 45 mg/kg/day) for two years showed a dose-dependent increase in thyroid hyperplasia and neoplasia (follicular adenoma/carcinoma). One-month and three-month studies in the rat have suggested that these results are linked to a nicardipine-induced reduction in plasma thyroxine (T4) levels with a consequent increase in plasma levels of thyroid stimulating hormone (TSH). Chronic elevation of TSH is known to cause hyperstimulation of the thyroid.

In rats on an iodine deficient diet, nicardipine administration for one month was associated with thyroid hyperplasia that was prevented by T4 supplementation.

Mice treated with nicardipine in the diet (at concentrations calculated to provide daily dosage levels of up to 100 mg/kg/day) for up to 18 months showed no evidence of neoplasia of any tissue and no evidence of thyroid changes.

There was no evidence of thyroid pathology in dogs treated with up to 25 mg nicardipine/kg/day for one year and no evidence of effects of nicardipine on thyroid function (plasma T4 and TSH) in man.

There was no evidence of a mutagenic potential of nicardipine in a battery of genotoxicity tests conducted on microbial indicator organisms, in micronucleus tests in mice and hamsters, or in a sister chromatid exchange study in hamsters.

No impairment of fertility was seen in male or female rats administered nicardipine at oral doses as high as 100 mg/kg/day (human equivalent dose about 16 mg/kg/day, 8 times the maximum recommended human oral dose).

13.3 Reproductive and Developmental Toxicology

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

14 CLINICAL STUDIES

Effects in Hypertension

In patients with mild-to-moderate chronic stable essential hypertension, nicardipine hydrochloride injection (0.5 to 4 mg/hr) produced dose-dependent decreases in blood pressure, although only the decreases at 4 mg/hr were statistically different from placebo. At the end of a 48-hour infusion at 4 mg/hr, the decreases were 26 mmHg (17%) in systolic blood pressure and 21 mmHg (20%) in diastolic blood pressure. In other settings (e.g., patients with severe or postoperative hypertension), nicardipine hydrochloride injection (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 less than or equal to 95 mmHg or greater or equal to 25 mmHg decrease and systolic blood pressure less than or equal to 160 mmHg, was 77 ± 5 minutes. The average maintenance dose was 8.0 mg/hr. The mean time to therapeutic response for postoperative hypertension, defined as greater than or equal to 15% reduction in diastolic or systolic blood pressure, was 12 minutes. The average maintenance dose was 3 mg/hr.

16 HOW SUPPLIED / STORAGE AND HANDLING

16.1 How Supplied

Nicardipine hydrochloride injection is available in packages as follows:

NDC	Strength	Packaged
0143-9689-10	25 mg/10 mL Single Dose Vial (2.5 mg/mL)	10 vials of 10 mL

Nicardipine Hydrochloride in 0.9% Sodium Chloride Injection is available in packages as follows:

NDC	Strength	Packaged
0143-9634-01	20 mg in 200 mL (0.1 mg/mL)	Flexible Containers
0143-9633-01	40 mg in 200 mL (0.2 mg/mL)	Flexible Containers

16.2 Storage and Handling

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Freezing does not adversely affect the product, but exposure to elevated temperatures should be avoided. Protect from light. Store vials in carton until used.

Manufactured by:
HIKMA FARMACÊUTICA (PORTUGAL), S.A.
Estrada do Rio da Mó, 8, 8A e 8B - Fervença - 2705-906 Terrugem SNT, PORTUGAL

Distributed by:
WEST-WARD PHARMACEUTICALS CORP.
Eatontown, NJ 07724
Revised April 2016

(b) (4)

USE IMMEDIATELY ONCE REMOVED FROM THE OVERWRAP

Nicardipine Hydrochloride
in 0.9% Sodium Chloride Injection

20 mg in 200 mL
(0.1 mg/mL)

Single Dose Container **200 mL Iso-osmotic**

Discard Unused Portion

Each mL contains 0.1 mg nicardipine hydrochloride in 9 mg Sodium Chloride, USP. Hydrochloric acid 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. Do not use unless solution is clear. Do not add supplemental medication. Must not be used in series connections.

STORAGE: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from freezing. Avoid excessive heat. **PROTECT FROM LIGHT, STORE IN CARTON UNTIL READY TO USE.**

For Intravenous Infusion

℞ Only

Sterile, Nonpyrogenic

WEST-WARD
PHARMACEUTICALS

Mfd. by: HIKMA FARMACÊUTICA (PORTUGAL), S.A.
Dist. by: WEST-WARD PHARMACEUTICAL CORP.
Eatontown, NJ 07724 USA

NDC 0143-9634-01

Article code

100%

(b) (4)

USE IMMEDIATELY ONCE REMOVED FROM THE OVERWRAP

Nicardipine Hydrochloride
in 0.9% Sodium Chloride Injection

40 mg in 200 mL
(0.2 mg/mL)

Single Dose Container **200 mL Iso-osmotic**

Discard Unused Portion

Each mL contains 0.2 mg nicardipine hydrochloride in 9 mg Sodium Chloride, USP. Hydrochloric acid 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. Do not use unless solution is clear. Do not add supplemental medication. Must not be used in series connections.

STORAGE: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from freezing. Avoid excessive heat. **PROTECT FROM LIGHT, STORE IN CARTON UNTIL READY TO USE.**

For Intravenous Infusion

DOUBLE CONCENTRATION: CHECK INFUSION RATE

℞ Only

Sterile, Nonpyrogenic

WEST-WARD
PHARMACEUTICALS

Mfd. by: HIKMA FARMACÊUTICA (PORTUGAL), S.A.
Dist. by: WEST-WARD PHARMACEUTICAL CORP.
Eatontown, NJ 07724 USA

NDC 0143-9633-01

Article code

100%

(b) (4)

TO OPEN – TEAR AT NOTCH ONE UNIT

Nicardipine Hydrochloride
in 0.9% Sodium Chloride Injection

20 mg in 200 mL
(0.1 mg/mL)

Single Dose Container **200 mL Iso-osmotic**

Discard Unused Portion

Each mL contains 0.1 mg nicardipine hydrochloride in 9 mg Sodium Chloride, USP. Hydrochloric acid 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. Do not use unless solution is clear. Do not add supplemental medication. Must not be used in series connections.

STORAGE: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from freezing. Avoid excessive heat. **PROTECT FROM LIGHT, STORE IN CARTON UNTIL READY TO USE.**

For Intravenous Infusion

℞ Only

Sterile, Nonpyrogenic

Mfd by: H KMA FARMACÊUT CA (PORTUGAL) S A
D st by: WEST WARD PHARMACEUTICAL CORP
Eatontown NJ 07724 USA

Article code NDC 0143 9634 01

Lot
Exp

(b) (4)

TO OPEN – TEAR AT NOTCH ONE UNIT

Nicardipine Hydrochloride
in 0.9% Sodium Chloride Injection
40 mg in 200 mL
(0.2 mg/mL)

Single Dose Container **200 mL Iso-osmotic**

Discard Unused Portion

Each mL contains 0.2 mg nicardipine hydrochloride in 9 mg Sodium Chloride, USP. Hydrochloric acid 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. Do not use unless solution is clear. Do not add supplemental medication. Must not be used in series connections.

STORAGE: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from freezing. Avoid excessive heat. **PROTECT FROM LIGHT, STORE IN CARTON UNTIL READY TO USE.**

DOUBLE CONCENTRATION: CHECK INFUSION RATE

For Intravenous Infusion

℞ Only

Sterile, Nonpyrogenic

Mfd by: H KMA FARMACÊUT CA (PORTUGAL) S A
D st by: WEST WARD PHARMACEUTICAL CORP
Eatontown NJ 07724 USA

Article code NDC 0143 9633 01

Lot

Exp

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022276Orig1s008

CROSS DISCIPLINE TEAM LEADER REVIEW

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Cross Disciplinary Review

NDA:	22-276 S008
Drug:	nicardipine hydrochloride injection
Indication:	short-term treatment of hypertension when oral therapy is not feasible or not desirable
Sponsor:	Exela Pharma Sciences, LLC
Review date:	July 23, 2013
Reviewer:	Thomas A. Marciniak, M.D. Medical Team Leader

Recommendation and Conclusions

I recommend a complete response for this submission because of the CMC, biopharmaceutics, and microbiology deficiencies noted below.

Materials Used in Review

1. CMC Review by Gurpret Gill-Sangha, Ph.D., dated July 22, 2013
2. Microbiology Review by Erika Pfeiler, Ph.D., dated July 12, 2013
3. Biopharmaceutics Review by Kelly Kitchens, Ph.D., dated July 3, 2013
4. NDA 22-276 S008 submission dated March 27, 2013

Background

We approved nicardipine hydrochloride injection on July 24, 2008, as a 505(b)(2) application rather than as an ANDA because we judged the formulation changes, benzoic acid replacing citric acid monohydrate (b) (4) and sodium chloride replacing sorbitol (b) (4), to be unacceptable for an ANDA. The original submission was for a 2.5 mg/mL vial for dilution. This submission is for a premixed 200 mL flexi-bag containing 0.1 or 0.2 mg/mL of the drug.

Chemistry, Manufacturing, and Controls (CMC)

The CMC reviewer, Dr. Gurpreet Gill-Sangha, recommends a complete response because the Establishment Evaluation System overall recommendation is still pending due to inconsistent information on sites provided, because of various discrepancies and incomplete specifications in the CMC data, and because of the recommendations of the biopharmaceutics and microbiology reviewers. Please see Dr. Gill-Sangha's review for the details. The CMD review also poses two questions for the clinical reviewer and team to evaluate that I address below under Clinical.

Biopharmaceutics

The biopharmaceutics reviewer, Dr. Kelly Kitchens, recommends a complete response because the listed drug product contains citric acid (anhydrous), sodium chloride, and

sorbitol whereas the proposed drug product contains only sodium chloride and pH adjusters as inactive ingredients. Dr. Kitchens requests evidence that the different composition does not affect the physiological disposition of the proposed drug product and hence does not recommend granting a waiver of *in-vivo* bioavailability/ bioequivalence studies.

Microbiology

The microbiology reviewer, Dr. Erika Pfeiler, recommends approvable pending a complete response to microbiology deficiencies. She records that the application does not clearly state (b) (4) and does not thoroughly describe (b) (4). She also has additional comments regarding the endotoxin limits. Please see her review for the details.

Nonclinical Pharmacology and Toxicology

There are no nonclinical pharmacology or toxicology data provided in this submission.

Clinical

There are no clinical or clinical pharmacology data provided in this submission. The clinical questions posed by the CMC review are the following:

1. The osmolality specification for the proposed 0.1 mg/mL and 0.2 mg/mL is (b) (4) mOsm/kg. The specification for approved 2.5 mg/mL is (b) (4) mOsm/kg. The specification for the proposed strengths is acceptable from the CMC perspective based on release and stability data provided from three lots each of 0.1 mg/mL and 0.2 mg/mL. Please evaluate from the clinical perspective if the proposed specification of osmolality is acceptable.

The proposed osmolality range is physiologic human plasma osmolality plus and minus about (b) (4) Such an osmolality range is desirable for a solution to be administered without further dilution.

2. Under the M2 section, 2.3.P, Exela compares their 0.1 and 0.2 mg/mL formulations to the EKR's 0.1 and 0.2 mg/mL and states that "While the above differences with respect to inactive ingredients are significant from a formulation perspective, they are not expected to affect the safety or efficacy of Exela's formulation in any material way". However, no rationale or data was provided to support the statement. Please evaluate from a clinical perspective if any data is required for support of the statement.

I show the sponsor's comparisons of the proposed formulations to the reference listed drug below.

Comparison of Exela's 0.1 mg/mL Drug Product with EKR Therapeutics Cardene I.V. Premixed Injection in 0.86% Sodium Chloride (0.1 mg/mL)

Ingredients	Exela's Formulation	EKR's Formulation[1]
Nicardipine Hydrochloride	0.1 mg/mL	0.1 mg/mL
Sodium Chloride, USP	9.0 mg/mL	8.6 mg/mL
Citric Acid, anhydrous, USP		0.0192 mg/mL
Sorbitol, NF		1.92 mg/mL
Hydrochloric Acid	pH to (b) (4)	pH to 3.7 – 4.7
Sodium Hydroxide		pH to 3.7 – 4.7
(b) (4)		

[1] Information regarding EKR Therapeutics Cardene I.V. Premixed Injection in 0.86% Sodium Chloride (0.1 mg/mL) formulation was obtained from the current package insert.

Comparison of Exela's 0.2 mg/mL Drug Product with EKR Therapeutics Cardene I.V. Premixed Injection in 0.83% Sodium Chloride (0.2 mg/mL)

Ingredients	Exela's Formulation	EKR's Formulation[1]
Nicardipine Hydrochloride	0.2 mg/mL	0.2 mg/mL
Sodium Chloride, USP	9.0 mg/mL	8.3 mg/mL
Citric Acid, anhydrous, USP		0.0384 mg/mL
Sorbitol, NF		3.84 mg/mL
Hydrochloric Acid	pH to (b) (4)	pH to 3.7 – 4.7
Sodium Hydroxide		pH to 3.7 – 4.7
(b) (4)		

[1] Information regarding EKR Therapeutics Cardene I.V. Premixed Injection in 0.86% Sodium Chloride (0.1 mg/mL) formulation was obtained from the current package insert.

From a clinical perspective the omission of citric acid, sodium hydroxide, and sorbitol should not affect the safety or efficacy of the nicardipine. All three are typical substances included or not included in a variety of IV products. I don't believe that there is a simple study that could demonstrate that the safety and efficacy of nicardipine are not affected, so I believe that we do have to rely upon clinical judgment in this instance.

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/s/

THOMAS A MARCINIAK
07/23/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022276Orig1s008

CHEMISTRY REVIEW(S)

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I (Branch III)
Review of Chemistry, Manufacturing, and Controls

1. **NDA number: 22276**

2. **Submission(s) Being Reviewed: S008**

Supplement Number	DARRTS SD Number	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
PAS	52	3/27/13	3/29/13	**6/7/13**	7/29/13	7/22/13

3. **Proposed Changes: New premixed formulations of 0.1 mg/mL and 0.2 mg/mL in new 200 mL Flexi-Bag containers**

4. **Review #: 2**

5. **Clinical Review Division:** Division of Cardiovascular and Renal Products, (CDER/ODE1/DCRP)

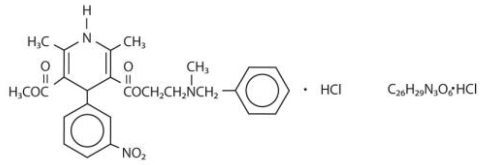
6. **Name and Address of Applicant:**
Exela Pharma Sciences, LLC
1325 Williams White Pl Northeast
PO Box 818
Lenoir, NC 28645
(828) 758-5474

7. **Drug Product:**

Proprietary Name	Nonproprietary Name (USAN) of Drug Substance	Indication	Dosage Form	Strength	Route of Administration
None	Nicardipine Hydrochloride Premixed injection	Calcium channel blocker for short-term treatment of hypertension	Injection	**Approved 2.5 mg/mL**, **Proposed** 0.1 mg/mL and 0.2 mg/mL	Intravenous infusion

Rx or OTC	Special Product?
Rx	-

8. **Chemical name and structure of drug substance:**



Chemical name: (±)-2-(benzyl-methyl amino) ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate monohydrochloride
Molecular formula: $C_{26}H_{29}N_3O_6.HCl$
MW: 515.99

9. Supporting/Relating Document: The following DMFs are related to this supplement:

- **DMF (b) (4) for (b) (4) by (b) (4) – Adequate as per Gurpreet Gill-Sangha, Ph.D. on July 22, 2013**
- **DMF (b) (4) for (b) (4) by (b) (4) – Inadequate as per Zedong Dong, Ph.D. on July 19, 2013**

10. Consults:

- **UPDATED EES overall recommendation acceptable (see attached EES report). However, due to discrepancy in the information provided on the manufacturing and control sites of drug substance and drug product, deficiency #I as outlined below still requires establishment information from the applicant.**
- **Biopharm review on July 12, 2013 by Kelly Kitchens, Ph.D., is Approvable pending a Complete Response**
- **Microbiology review on July 12, 2013 by Erika Pfeiler, Ph.D. is Approvable pending a Complete Response**

11. Summary/Remarks: NA

12. Conclusions & Recommendations: Recommend Complete Response.

13. Comments/Deficiencies to be Conveyed to Applicant: The following are to be conveyed to the applicant in a Complete Response letter.

I. There is a discrepancy in the information submitted in this supplement and that provided on July 2, 2013 response via email regarding the manufacturing and controls sites for the proposed strengths. Provide a list of all manufacturing and controls (release as well as stability testing) sites to be used for manufacture and control of the proposed strengths and their responsibilities. Include appropriate information such as FEI #, address, contact person, phone number, etc.

II. On June 27, 2013 we requested that you clarify for all sections of Drug Substance and Drug Product, the differences between the approved 2.5 mg/mL formulation and the proposed 0.1 mg/mL and 0.2 mg/mL. We requested that you include information related to composition, manufacturing sites, release and stability specifications, container closure system and stability data to support expiration dating. It was also stated that the information could be provided in a tabular format with hyperlinks for different sections to delineate any differences.

However, you responded on July 2, 2013, with a summary data of composition, manufacturing sites, release and stability specifications for drug substance and drug product.

Based on the data provided in the supplement and the July 2, 2013 summary tables, please clarify for the following:

- **Impurity specification for [redacted] (Impurity [redacted] as NMT [redacted]% is not supported by release and stability data provided. The approved limit for Impurity [redacted] is NMT [redacted]%. Provide data to justify increasing the limit from NMT [redacted]% to NMT [redacted]% based on data.**

- **Similarly [redacted] (Impurity [redacted] shows out of specifications (OOS) results at 6 month time point at accelerated conditions of 40 °C. However, this impurity [redacted] is within limits at the intermediate condition of 30 °C. Provide additional long-term and intermediate condition (30 °C) stability data to support the shelf-life of the product since Impurity [redacted] is OOS at 40 °C conditions.**

- **Justify the specification of NMT [redacted]% for [redacted] which is a new specification proposed for these proposed strengths in the new flexibags. The limits are not supported by stability data which shows levels NMT [redacted]% even at accelerated conditions.**

- **An impurity listed as [redacted] with a proposed specification of [redacted] is monitored during stability studies of the drug product. This impurity is not listed as part of the proposed release and stability specifications. Please provide details on this impurity and propose specifications related to this impurity in the drug product release and stability specifications based on data.**

III. **Based on the data provided in Section 32p7 for container closure extractable and leachables, please provide data that show the amount of extractables and leachables are at a safe limit.**

IV. **In your response dated July 2, 2013, you stated that the stability studies were conducted using the proposed commercial container closure. However, when requested a sample of the bag used on June 26, 2013, you stated that the bags were not yet manufactured. Please clarify this discrepancy and provide a sample of the bag.**

The following comments are for the clinical reviewer and team to evaluate:

1. **The osmolality specification for the proposed 0.1 mg/mL and 0.2 mg/mL is [redacted] mOsm/kg. The specification for approved 2.5 mg/mL is [redacted] mOsm/kg. The specification for the proposed strengths is acceptable from the CMC perspective based on release and stability data provided from three lots each of 0.1 mg/mL and 0.2 mg/mL. Please evaluate from the clinical perspective if the proposed specification of osmolality is acceptable.**

2. **Under the M2 section, 2.3.P, Exela compares their 0.1 and 0.2 mg/mL formulations to the EKR's 0.1 and 0.2 mg/mL and states that "***While the above differences with respect to inactive ingredients are significant from a formulation perspective, they are not expected to affect the safety or efficacy of Exela's formulation in any material way***".**

However, no rationale or data was provided to support the statement. Please evaluate from a clinical perspective if any data is required for support of the statement.

V. **Primary Reviewer:** Gurpreet Gill-Sangha, Ph.D., CMC reviewer, ONDQA

Secondary Reviewer: Hasmukh Patel, Ph.D., Branch Chief, Branch III, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

(See appended electronic signature page)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 22276/008	**Action Goal:**	
Stamp Date:	29-MAR-2013	**District Goal:**	24-JUN-2013
Regulatory:	29-JUL-2013		
Applicant:	EXELA PHARMA SCIENCE	**Brand Name:**	NICARDIPINE HYDROCHLORIDE INJECTION
	1325 WILLIAM WHITE PL NORTHEAST	**Estab. Name:**	
	LENOIR, NC 28645	**Generic Name:**	NICARDINE
Priority:	5S	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	110	001; SOLUTION, INJECTION; NICARDIPINE HYDROCHLORIDE; 25MG/10ML	

Application Comment:

FDA Contacts:	G. GILL SANGHA	Prod Qual Reviewer		3017963879
	B. RILEY	Micro Reviewer	(HFD-805)	3017961595
	Y. KNIGHT	Product Quality PM		3017962133
	M. MONTELEONE	Regulatory Project Mgr	(HFD-110)	3017961952
	N. CHIDAMBARAM	Team Leader		3017961339

Overall Recommendation:	ACCEPTABLE	on 23-JUL-2013	by J. WILLIAMS	()	3017964196
	PENDING	on 07-JUN-2013	by EES_PROD		
	PENDING	on 07-JUN-2013	by EES_PROD		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** **FEI:** 3008563008

EXELA PHARMA SCIENCES

1325 WILLIAM WHITE PLACE NE
LENOIR, NC 28645

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment Comment: MANUFACTURE, FORMULATION DEVELOPMENT, FILING AGENT, RELEASE TESTING OF DRUG SUBSTANCE, DRUG PRODUCT, EXCIPIENT TESTING, AND STABILITY TESTING (on 07-JUN-2013 by Y. KNIGHT () 3017962133)

Profile: (b) (4) SMALL VOLUME PARENTERAL DRUG **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	07-JUN-2013				KNIGHTY
SUBMITTED TO DO	08-JUN-2013	10-Day Letter			WILLIAMSJU
DO RECOMMENDATION	23-JUL-2013			ACCEPTABLE	LTHOMAS
A PRE-APPROVAL AND GMP INSPECTION OF THE FIRM WAS CONDUCTED (b) (4) NO FORM FDA 483 WAS ISSUED TO FIRM MANAGEMENT AND THE INSPECTION WAS CLASSIFIED NAI. PRODUCT SPECIFIC COVERAGE OF THE SUBJECT DRUG PRODUCTS FOR ANDA (b) (4) AND ANDA (b) (4) OCCURRED WITH NO REMARKABLE FINDINGS NOTED. THE PROFILE CLASS (b) (4) WAS FOUND ACCEPTABLE.				INSPECTION	
BASED ON THE INSPECTION RESULTS, THE DISTRICT RECOMMENDS APPROVAL OF THE FIRM FOR ITS LISTED RESPONSIBILITY IN THE APPLICATION.					
OC RECOMMENDATION	23-JUL-2013			ACCEPTABLE	WILLIAMSJU
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: RELEASE TESTING OF DRUG SUBSTANCE AND EXCIPIENT TESTING (on 07-JUN-2013 by Y. KNIGHT () 3017962133)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	07-JUN-2013				KNIGHTY
OC RECOMMENDATION	08-JUN-2013			ACCEPTABLE BASED ON PROFILE	WILLIAMSJU

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: RELEASE TESTING OF DRUG SUBSTANCE (b) (4) (on 07-JUN-2013 by Y. KNIGHT () 3017962133)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	07-JUN-2013				KNIGHTY
OC RECOMMENDATION	08-JUN-2013			ACCEPTABLE BASED ON PROFILE	WILLIAMSJU

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/s/

GURPREET K GILL SANGHA
07/24/2013
Review #2 for N22276/S008

HASMUKH B PATEL
07/24/2013

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I (Branch III)
Review of Chemistry, Manufacturing, and Controls

1. **NDA number: 22276**

2. **Submission(s) Being Reviewed: S008**

Supplement Number	DARRTS SD Number	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
PAS	52	3/27/13	3/29/13	**6/7/13**	7/29/13	7/22/13

3. **Proposed Changes: New premixed formulations of 0.1 mg/mL and 0.2 mg/mL in new 200 mL Flexi-Bag containers**

4. **Review #: 1**

5. **Clinical Review Division:** Division of Cardiovascular and Renal Products, (CDER/ODE1/DCRP)

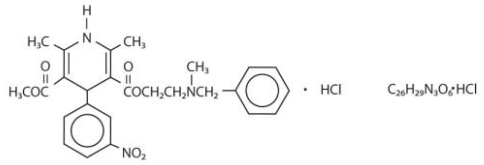
6. **Name and Address of Applicant:**
Exela Pharma Sciences, LLC
1325 Williams White Pl Northeast
PO Box 818
Lenoir, NC 28645
(828) 758-5474

7. **Drug Product:**

Proprietary Name	Nonproprietary Name (USAN) of Drug Substance	Indication	Dosage Form	Strength	Route of Administration
None	Nicardipine Hydrochloride Premixed injection	Calcium channel blocker for short-term treatment of hypertension	Injection	**Approved 2.5 mg/mL**, **Proposed** 0.1 mg/mL and 0.2 mg/mL	Intravenous infusion

Rx or OTC	Special Product?
Rx	-

8. **Chemical name and structure of drug substance:**



Chemical name: (±)-2-(benzyl-methyl amino) ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate monohydrochloride
Molecular formula: $C_{26}H_{29}N_3O_6.HCl$
MW: 515.99

9. Supporting/Relating Document: The following DMFs are related to this supplement:

- **DMF (b) (4) for (b) (4) by (b) (4) – Adequate as per Gurpreet Gill-Sangha, Ph.D. on July 22, 2013**
- **DMF (b) (4) for (b) (4) by (b) (4) – Inadequate as per Zedong Dong, Ph.D. on July 19, 2013**

10. Consults:

- **EES overall recommendation pending due to inconsistent information on sites provided**
- **Biopharm review on July 12, 2013 by Kelly Kitchens, Ph.D., is Approvable pending a Complete Response**
- **Microbiology review on July 12, 2013 by Erika Pfeiler, Ph.D. is Approvable pending a Complete Response**

11. Summary/Remarks: NA

12. Conclusions & Recommendations: Recommend Complete Response and EES still pending.

13. Comments/Deficiencies to be Conveyed to Applicant: The following are to be conveyed to the applicant in a Complete Response letter.

I. There is a discrepancy in the information submitted in this supplement and that provided on July 2, 2013 response via email regarding the manufacturing and controls sites for the proposed strengths. Provide a list of all manufacturing and controls (release as well as stability testing) sites to be used for manufacture and control of the proposed strengths and their responsibilities. Include appropriate information such as FEI #, address, contact person, phone number, etc.

II. On June 27, 2013 we requested that you clarify for all sections of Drug Substance and Drug Product, the differences between the approved 2.5 mg/mL formulation and the proposed 0.1 mg/mL and 0.2 mg/mL. We requested that you include information related to composition, manufacturing sites, release and stability specifications, container closure system and stability data to support expiration dating. It was also stated that the information could be provided in a tabular format with hyperlinks for different sections to delineate any differences.

However, you responded on July 2, 2013, with a summary data of composition, manufacturing sites, release and stability specifications for drug substance and drug product.

Based on the data provided in the supplement and the July 2, 2013 summary tables, please clarify for the following:

- **Impurity specification for [redacted] (Impurity [redacted] as NMT [redacted]% is not supported by release and stability data provided. The approved limit for Impurity [redacted] is NMT [redacted]%. Provide data to justify increasing the limit from NMT [redacted]% to NMT [redacted]% based on data.**

- **Similarly [redacted]" (Impurity [redacted]) shows out of specifications (OOS) results at 6 month time point at accelerated conditions of 40 °C. However, this impurity [redacted] is within limits at the intermediate condition of 30 °C. Provide additional long-term and intermediate condition (30 °C) stability data to support the shelf-life of the product since Impurity [redacted] is OOS at 40 °C conditions.**

- **Justify the specification of NMT [redacted]% for [redacted] which is a new specification proposed for these proposed strengths in the new flexibags. The limits are not supported by stability data which shows levels NMT [redacted]% even at accelerated conditions.**

- **An impurity listed as [redacted] with a proposed specification of [redacted]" is monitored during stability studies of the drug product. This impurity is not listed as part of the proposed release and stability specifications. Please provide details on this impurity and propose specifications related to this impurity in the drug product release and stability specifications based on data.**

III. **Based on the data provided in Section 32p7 for container closure extractable and leachables, please provide data that show the amount of extractables and leachables are at a safe limit.**

IV. **In your response dated July 2, 2013, you stated that the stability studies were conducted using the proposed commercial container closure. However, when requested a sample of the bag used on June 26, 2013, you stated that the bags were not yet manufactured. Please clarify this discrepancy and provide a sample of the bag.**

The following comments are for the clinical reviewer and team to evaluate:

1. **The osmolality specification for the proposed 0.1 mg/mL and 0.2 mg/mL is [redacted] mOsm/kg. The specification for approved 2.5 mg/mL is [redacted] mOsm/kg. The specification for the proposed strengths is acceptable from the CMC perspective based on release and stability data provided from three lots each of 0.1 mg/mL and 0.2 mg/mL. Please evaluate from the clinical perspective if the proposed specification of osmolality is acceptable.**

2. **Under the M2 section, 2.3.P, Exela compares their 0.1 and 0.2 mg/mL formulations to the EKR's 0.1 and 0.2 mg/mL and states that "***While the above differences with respect to inactive ingredients are significant from a formulation perspective, they are not expected to affect the safety or efficacy of Exela's formulation in any material way***".**

However, no rationale or data was provided to support the statement. Please evaluate from a clinical perspective if any data is required for support of the statement.

V. **Primary Reviewer:** Gurpreet Gill-Sangha, Ph.D., CMC reviewer, ONDQA

Secondary Reviewer: Hasmukh Patel, Ph.D., Branch Chief, Branch III, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

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/s/

GURPREET K GILL SANGHA
07/22/2013
CMC Review #1 for N22276/S008

HASMUKH B PATEL
07/22/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022276Orig1s008

PHARMACOLOGY REVIEW(S)

MEMORANDUM

Date: April 4, 2016

From: Thomas Papoian, PhD, DABT
Supervisory Pharmacologist

To: NDA 22-276/S-008
Nicardipine Hydrochloride Injection and
Nicardipine Hydrochloride in 0.9% Sodium Chloride Injection

Sponsor: Excela Pharma Sciences, LLC; Lenoir, NC

Subject: Addendum to Previous Review (dated March 24, 2016):
"Review of container closure extractable and leachables data to determine if they are at a safe level"

1. Background

In a previous review (dated 3/24/16), a request was sent to the sponsor for additional information:

The Study Report titled "Extractables Study on [redacted (b) (4)] (Report No. TE 06155) did not appear to specify the number of bag units represented by 25 gms of test material extracted. Without this information, it is difficult to determine the number of bags represented by 25 gms of test material, and how to convert final results in mg/kg to total daily dose under therapeutic conditions of use. If this information was present, please direct us to where in the study report it is located. Otherwise, please provide this information.

The sponsor replied with the following information (dated April 4, 2016):

To determine the number of 200 Liter [redacted (b) (4)] bags represented by 25 grams of test material [redacted (b) (4)] the weight of a known quantity of [redacted (b) (4)] was determined.

[redacted (b) (4)]

None of the extractable or leachable components, including any toxic metals, appear to be at levels high enough to cause undue concern, and are well below safety thresholds for such compounds. Generally, safety thresholds based on existing EPA databases of chemicals employ levels of 5 µg/day for general non-carcinogenic toxins (Ball et al., Toxicol. Sci., 2007) to as low as 1.5 µg/day for genotoxins (per ICH-M7 guidelines). However, for acute indications (≤ 1 month), such as the current short-term (≤48 hours) use of intravenous nicardipine, levels of up to 120 µg/day of a genotoxic compound are allowed.

Based on this latest information supplied by the sponsor, there are no safety concerns from a pharmacology or toxicology perspective.

Thomas Papoian, PhD, DABT
Supervisory Pharmacologist

Results: The results of the headspace-GC/MS analysis are summarized in Table 6 ((b) (4) Table 4):

Table 6 (b) (4) Table 4)

(b) (4)

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/s/

THOMAS PAPOIAN
04/04/2016

MEMORANDUM

Date: March 24, 2016

From: Thomas Papoian, PhD, DABT
Supervisory Pharmacologist

To: NDA 22-276/S-008
Nicardipine Hydrochloride Injection and
Nicardipine Hydrochloride in 0.9% Sodium Chloride Injection

Sponsor: Excela Pharma Sciences, LLC; Lenoir, NC

Subject: Review of container closure extractable and leachables data to determine if they are at a safe level

1. Background

Nicardipine (Cardene®) is a calcium channel blocker that was approved in 1992 for treatment of angina pertoris and hypertension (NDA 19-734). The pharmacological mechanism is due to inhibition of the transmembrane influx of calcium ions into cardiac muscle and smooth muscle that results in muscle relaxation. The drug effects are more preferential to smooth muscle than to cardiac muscle.

Nicardipine hydrochloride injection was first approved in 1988 (NDA 19-488), and is indicated for the short-term treatment of hypertension when oral therapy is not feasible. The current NDA 22-276 is a pre-mixed 10 ml solution of 25 mg/vial nicardipine (2.5 mg/ml) for intravenous injection at 0.1 mg/ml final strengths following dilution with 240 ml of one of the following diluents:

Dextrose (5%) Injection, USP
Dextrose (5%) and Sodium Chloride (0.45%) Injection, USP
Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP
Dextrose (5%) with 40 mEq Potassium, USP
Sodium Chloride (0.45%) Injection, USP

Nicardipine Hydrochloride in 0.9% Sodium chloride Injection is supplied as a single-use, ready-to-use, iso-osmotic solution for intravenous administration in a 200 ml flexible container with 20 mg (0.1 mg/mL) or 40 mg (0.2 mg/mL) nicardipine hydrochloride in sodium chloride. No further dilution is needed.

Dosing is individualized depending on the severity of hypertension and the response of the patient during dosing. Dosing is initiated at a rate of 50 ml/hr (5 mg/hr). If desired blood pressure reduction is not achieved at this dose, the infusion rate is then increased by 25 ml/hr (2.5 mg/hr) every 15

minutes up to a maximum of 150 ml/hr (15 mg/hr), until desired blood pressure reduction is achieved. Based on the label, the duration of dosing in conducted clinical trials varied from a few minutes to 48 hours.

For the current NDA 22-276, the applicant received a deficiency letter (dated 7/25/2013) outlining several deficiencies in Product Quality. One item was stated as follows:

"4. Based on the data provided in Section 32p7 for container closure extractable and leachables, please provide data that show the amount of extractables and leachables are at a safe limit."

In their response (dated 12/4/2015), the applicant referenced the extractable and leachable testing results and the associated extractable and leachable characteristics that were provided in [redacted] Drug Master File, Type III # [redacted]. They also provided two study reports, one for the [redacted] and one for the [redacted] bag, that supposedly are part of the single-use, ready-to-use, iso-osmotic solution (nicardipine in 0.9% sodium chloride). The study reports were submitted to the DMF and evaluated extractables and leachables using model solvents which bracket and are worst case compared to the drug product solution. These data are reviewed below.

2. Review of Study Reports

2.1. Determination of the Extractable [redacted]

Report Number: TE 09034
Study Number: 09-B0071 and 09-B0072
Conducting Lab: [redacted]
QA'd: Yes
Date of Report: May 18, 2009

Purpose: To identify [redacted] additives, impurities and degradation products present in and on [redacted]

Methods: Two different methods were applied to release compounds:

A. Neat test item: sample directly analyzed without solvent extraction
B. Reflux extraction in Water For Injection (WFI)
The extract without test article was used as control.

[redacted]

(b) (4)

The extracts were subjected to the following analytical methods:

1. Headspace Gas Chromatography 1 Mass Spectrometry (HS -GC/MS) to determine volatile organic compounds (VOCl).
2. Gas Chromatography 1 Mass Spectrometry (GC/MS) to determine semi-volatile organic compounds (SVOC).
3. Liquid Chromatography 1 Mass Spectrometry (LC/MS) to determine non-volatile organic compounds (NVOC).
4. Inductive Coupled Plasma 1 Optical Emission Spectroscopy (ICP/OES) for element analysis.
5. Ion Chromatography (IC) for the detection of anions.
6. Determination of the Total Organic Carbon (TOC).

Data were evaluated against a Mass Spectral Library of >190,000 compounds, and identified according to best fit.

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3. Overall Summary and Discussion

Various compounds were identified after extraction of various quantities of test [redacted] material in various volumes of water and other organic solvents. Results of detected compounds were expressed in terms of mg/kg extracted compound to weight of test material.

Previous experiences with extractables and leachables have focused on compounds with known safety risk, such as bisphenol A (a known teratogen), benozophenone (a known photo initiator), and nitrosamines and PVC monomers (known carcinogens). Once compounds of known or suspected safety risk are identified, subsequent nonclinical studies may be performed to identify safe levels for the intended route of administration, intravenous in this case. Studies may include in vitro genotoxicity studies or studies in animals for ≥3 months. Generally, safety thresholds based on existing EPA databases of chemicals employ levels of 5 µg/day for general non-carcinogenic toxins (Ball et al., Toxicol. Sci., 2007) to as low as 1.5 µg/day for genotoxins (per ICH-M7 guidelines). However, for acute indications (≤ 1 month), such as the current short-term (≤48 hours) use of intravenous nicardipine, levels of up to 120 µg/day of a genotoxic compound are allowed.

For any identified compounds above the 1.5 µg/day threshold, a structural-activity relationship (QSAR) analyses can be conducted for structural alert(s) for genetic toxicity. For those compounds identified above the 5 µg/day threshold and of suspected toxic potential, qualification studies in animals of 3 months duration may be requested.

3.1. [redacted]

For the [redacted], one unit = [redacted]. According to the current label, nicardipine can be administered at a maximum rate of 150 ml/hr with clinical trial durations of up to 48 hours **(= 7200 ml total**). Although this high volume is unlikely to occur in a normal clinical setting, it is a worst case scenario. This is equivalent to 36 bags/48 hours or 18 bags/day = [redacted] gms of material/day. To obtain actual levels of compounds expressed as mg/kg of original test material, results were multiplied by [redacted] (= [redacted] gms divided by 1 kg or 1000 gms) to obtain maximum possible levels of extractable compounds likely to be leached and administered in a 24 hour period.

Results in Table 1 ([redacted] Table 5) for Headspace-GC/MS analysis for volatiles showed elevated levels the following compounds:

[redacted]

Results in Table 2 ([redacted] Table 6) for semi volatile organic compounds did not show levels greater than [redacted] mg/kg x [redacted] = [redacted] mg = [redacted] µg/day.

Results in Table 3 ([redacted] Table 7) for non-volatile organic compounds found [redacted] at levels above detectable limits ([redacted] mg/kg x [redacted] = [redacted] mg/day – [redacted] µg/day). According to the sponsor, this compound is an [redacted] product of [redacted] found together with [redacted]

[redacted] It is intended to [redacted].

Results in Table 4 ([redacted] Table 8) for metals found [redacted] above detectable limits:

[redacted] mg/kg x [redacted] = [redacted] mg/day = [redacted] µg/day.
[redacted] mg/kg x [redacted] = [redacted] mg/day = [redacted] µg/day.

All of these extracted compounds appear within accepted limits. [redacted] are considered Class 3 solvents, according to ICH-Q3C (Nov 2003), and should be kept to 50 mg per day or less, which is the case here.

In the case of [redacted] it does not appear to be listed in the ICH-Q3C Tables and List Guidance (Nov. 2003) with any known toxicity. Further, according to commercially available safety data sheets [redacted]

[redacted]

In the case of [redacted], it is considered a Class 3 element (according to ICH-Q3D; Sept. 2015) with relatively low toxicity. It was a high permissible daily exposure (PDE) of >500 µg/day when given by the oral route, but may be lower when given parenterally. The levels of [redacted] µg/day given IV appear to be well within safe limits.

3.2. Bag

[redacted], results were expressed as mg extracted compound per kg of bag material. Extracts were prepared from 25 gms of test substance in 500 ml water. <u>However, it is not clear how many bags is represented by 25 gms.</u> For a maximum daily infusion volume of 3600 ml (=7200 ml/48 hours) a maximum number of 18-200 ml single-use, ready-to-use bags would be needed per day. Without knowing the weight of each individual bag, it is difficult to determine the number of bags represented by 25 gms of test material, and how to convert final results in mg/kg to total daily dose.

However, based on the test results of the headspace-GC/MS analysis (Table 6; [redacted] Table 4), results of the GC/MS analysis (Table 7; [redacted]s Table 5), results of the LC/MS-analysis of the WFI extract (Table 8; [redacted] Table 6), and metals concentrations in the WFI-extract (Table 9;

[redacted] Table 7), none of the compounds or elements listed were at levels sufficiently elevated to present a safety risk. In the case of metals, ICH-Q3D (Sept. 2015) lists relatively low PDE's (<15 µg/day) for Class 1 metals (Cd, Pb, As, Hg) when given parenterally. [redacted] the applicant should be asked to clarify the weight of individual 200 ml single-use, ready-to-use bags, so that a proper and final safety evaluation can be made.

4. Recommendations

Internal

The submitted data on levels of extractable and/or leachable compounds from the [redacted] and [redacted] bag were reviewed to determine if they were at acceptable safe levels when nicardipine is diluted into physiological solutions (saline or dextran in saline) for intravenous administration of volumes up to a maximum of 7200 ml over 48 hours (= 3600 mg/day).

For the [redacted], all compounds extracted appeared to be at relatively safe levels for therapeutic conditions of use. However, one compound in particular [redacted], was at levels that would result in a daily dose of [redacted] µg/day.

[redacted]

For the bag data, results were expressed as mg extracted compound per kg of bag material, but it was not clear how many bags is represented by the 25 gms amount extracted. Without this information, it is difficult to determine the number of bags represented by 25 gms of test material, and how to convert final results in mg/kg to total daily dose. However, based on the test results, none of the compounds or elements listed were at levels sufficiently elevated to present a safety risk. Regardless, the applicant should be asked to clarify the weight of individual 200 ml single-use, ready-to-use bags, so that a proper and final safety evaluation can be made.

To the Applicant

The Study Report titled "Extractables Study on [redacted] (Report No. TE 06155) did not appear to specify the number of bag units represented by 25 gms of test material extracted. Without this information, it is difficult to determine the number of bags represented by 25 gms of test material, and how to convert final results in mg/kg to total daily dose under therapeutic conditions of use. If this information was present, please direct us to where in the study report it is located. Otherwise, please provide this information.

Thomas Papoian, PhD, DABT
Supervisory Pharmacologist

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/s/

THOMAS PAPOIAN
03/24/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022276Orig1s008

MICROBIOLOGY/VIROLOGY REVIEW(S)

Product Quality Microbiology Review

12 July 2013

NDA: 22276/S008

Drug Product Name
Proprietary: N/A
Non-proprietary: Nicardipine Hydrochloride Premixed Injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
27 MAR 2013	29 MAR 2013	07 JUN 2013	17 JUN 2013
10 JUL 2013	11 JUL 2013	N/A	N/A

Applicant/Sponsor
Name: Exela Pharma Sciences, LLC
Address: 1325 William White Place, P.O. Box 818, Lenoir, NC 28645
Representative: Jonathan Sterling
Telephone: 828-758-5474

Name of Reviewer: Erika Pfeiler, Ph.D.

Conclusion: Recommended as Approvable Pending a Complete Response to Microbiology Deficiencies

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: PAS

2. SUBMISSION PROVIDES FOR: The addition of a 200 ml flexi-bag presentation containing 0.1 and 0.2 mg/ml of Nicardipine Hydrochloride

3. MANUFACTURING SITE: (b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- 200 ml (b) (4) bags
- 0.1 and 0.2 mg/ml Nicardipine Hydrochloride in 0.9% saline
- Intravenous infusion

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Short-term treatment of hypertension

B. SUPPORTING/RELATED DOCUMENTS:

Microbiology Review 1 of NDA 22276, DARRTS Date 31 March 2008

C. REMARKS:

This supplemental application proposes 200 ml flexi-bag presentations containing 0.1 mg/ml or 0.2 mg/ml of Nicardipine Hydrochloride. A 2.5 mg/ml presentation of the drug product in a vial was previously approved.

A second information request was submitted to the applicant on 10 July 2013 (see DARRTS for IR text.) However, due to the limited time before the PDUFA date for this supplement, the division PM requested that the review be finalized prior to receipt of the response to this IR.

filename: N22276S008R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommended as Approvable Pending a Complete Response to Microbiology Deficiencies.

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 – Drug product is (b) (4) (b) (4)

B. Brief Description of Microbiology Deficiencies – Application does not clearly state (b) (4)

C. Assessment of Risk Due to Microbiology Deficiencies – The deficiencies give a low risk of release of a nonsterile drug product.

D. Contains Potential Precedent Decision(s)- ☐ **Yes** ☒ **No**

III. Administrative

A. Reviewer's Signature _____

Erika Pfeiler, Ph.D.
Microbiologist

B. Endorsement Block_____

Bryan Riley, Ph.D.
Microbiology Team Leader

C. CC Block
N/A

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/s/

ERIKA A PFEILER
07/12/2013

BRYAN S RILEY
07/12/2013
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022276Orig1s008

CLINICAL PHARMACOLOGY REVIEW(S)

BIOPHARMACEUTICS REVIEW - ADDENDUM Office of New Drug Quality Assessment			
Application No.:	NDA 22276/PAS-008	**Reviewer:** Kelly M. Kitchens, Ph.D.	
Submission Date:	March 27, 2013		
Division:	Division of Cardiovascular and Renal Products	**Team Leader:** Angelica Dorantes, Ph.D.	
Applicant:	Exela Pharma Sciences, LLC	**Acting Supervisor:** Richard Lostritto, Ph.D.	
Trade Name:	None proposed	**Date Assigned:**	June 14, 2013
Established Name:	Nicardipine Hydrochloride Premixed Injection	**Date of Review:**	July 22, 2013
Indication:	Short-term treatment of hypertension when oral therapy is not feasible.	**Type of Submission:** Prior Approval Supplement	
Formulation/ strengths	Injectable/ 0.1 mg/mL and 0.2 mg/mL		
Route of Administration	Intravenous Infusion		
Type of Review:	Biowaiver Request		

SYNOPSIS

Background: In the original Supplement S-008 to **NDA 22276** dated March 27, 2013, the Applicant submitted a biowaiver request for Nicardipine Hydrochloride Premixed Injection, 0.1 mg/mL and 0.2 mg/mL relying on the FDA's safety and efficacy findings for **NDA 19734** for Cardene I.V. (nicardipine hydrochloride) Premixed Injection, 0.1 mg/mL and 0.2 mg/mL. Note that in the Original Biopharmaceutics review dated 7/12/13, the biowaiver request was NOT granted due to the lack of complete supportive information justifying the formulation differences between the proposed product and the reference listed product approved under NDA 19734.

Review: This review is an addendum to the Original Biopharmaceutics Review for NDA 022276/S008 by Dr. Kelly Kitchens, dated July 12, 2013 in DARRTS.

In this addendum, Biopharmaceutics is revising its previous recommendation for the biowaiver request. For this revision, Biopharmaceutics is taking into consideration that the biowaiver request was submitted under a supplement to NDA 22276, rather than a 505(b)(2) submission and therefore from the regulatory perspective, it is more appropriate that the biowaiver request relies on the efficacy/safety findings of the Nicardipine Hydrochloride Injection (2.5 mg/mL) product approved under the same NDA 22276.

Therefore, when the approved Nicardipine Hydrochloride Injection is diluted with 240 mL Sodium Chloride (0.9%) Injection, USP, it has the same formulation in the same concentration as the proposed Nicardipine Hydrochloride Premixed Injection, 0.1 mg/mL (which includes Sodium Chloride, USP, as an inactive ingredient) and therefore the CFR's formulation requirements for granting a biowaiver are fulfilled.

Unit Composition for Nicardipine Hydrochloride Injection

Ingredients	Approved Strength 2.5 mg/mL	Proposed Strength 0.2 mg/mL	Proposed Strength 0.1 mg/mL
Nicardipine Hydrochloride	2.5	0.2	0.1
Sodium Chloride, USP	7.5	9.0	9.0
Benzoic Acid, USP	0.305	---	---
Hydrochloric Acid	---	Adjust pH (b) (4)	Adjust pH (b) (4)
Sodium Hydroxide, NF	~0.009*	---	---
(b) (4)			

Per the approved label for Nicardipine Hydrochloride Injection (2.5 mg/mL), each vial (25 mg) should be diluted with 240 mL of compatible intravenous fluid:

- Dextrose (5%) Injection, USP
- Dextrose (5%) and Sodium Chloride (0.45%) Injection, USP
- Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP
- Dextrose (5%) with 40 mEq Potassium, USP
- Sodium Chloride (0.45%) Injection, USP
- Sodium Chloride (0.9%) Injection, USP

RECOMMENDATION:

The waiver for *in-vivo* bioavailability/bioequivalence studies for Nicardipine Hydrochloride Premixed Injection, 0.1 mg/mL and 0.2 mg/mL, in 0.9% Sodium Chloride is granted. For additional details, refer to the Biopharmaceutics Review[1] for NDA 22276/S-008.

From the Biopharmaceutics perspective, NDA 22276/S-008 for Nicardipine Hydrochloride Premixed Injection, 0.1 mg/mL and 0.2 mg/mL, in 0.9% Sodium Chloride is recommended for approval.

Signature
Kelly M. Kitchens, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Signature
Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc. RLostritto.

[1] DARRTS: NDA 022276, Submit/Final Date: 07/12/2013, KITCHENS, KELLY M, REV-QUALITY-21(Primary Reviewer), Supplement-8 (Manufacturing (CMC)).

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/s/

KELLY M KITCHENS
07/24/2013

ANGELICA DORANTES
07/24/2013

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 22276/S008	**Reviewer:** Kelly M. Kitchens, Ph.D.	
Submission Date:	March 27, 2013		
Division:	Division of Cardiovascular and Renal Products	**Team Lead:** Angelica Dorantes, Ph.D.	
Applicant:	Exela Pharma Sciences, LLC	**Acting Supervisor:** Richard Lostritto, Ph.D.	
Trade Name:	None proposed	**Date Assigned:**	June 14, 2013
Established Name:	Nicardipine Hydrochloride Premixed Injection	**Date of Review:**	July 3, 2013
Indication:	Short-term treatment of hypertension when oral therapy is not feasible.	**Type of Submission:** CMC Supplement	
Formulation/ strengths	Injectable/ 0.1 mg/mL and 0.2 mg/mL		
Route of Administration	Intravenous Infusion		
Type of Review:	Biowaiver Request		

SUMMARY:

Background: Nicardipine Hydrochloride Injection, 25 mg/vial, was approved on July 24, 2008. The ownership of the NDA was transferred from Teva Parenteral Medicines, Inc. to Exela Pharma Sciences, LLC, effective May 28, 2010. The Applicant requests approval of two new drug products, Nicardipine Hydrochloride Premixed Injection, 0.1 mg/mL and 0.2 mg/mL, in 0.9% Sodium Chloride. Reference is made to pIND (b) (4) filed on June 27, 2011for Nicardipine Hydrochloride Premixed Injection. A pIND meeting was requested to discuss the appropriateness of the 505(b)(2) pathway for the proposed drug product. The following meeting preliminary comments were conveyed to the Applicant for pIND (b) (4),[1] and the Applicant did not require further discussion on the preliminary comments:

- The proposal to rely on FDA's previous safety and efficacy findings for Cardene I.V. Premixed Injection (NDA 19734) to submit a 505(b)(2) application seems acceptable based on the information provided.
- The proposal to submit a single, 505(b)(2) supplement is acceptable based on the

[1] DARRTS: IND- (b) (4) MONTELEONE, MICHAEL V, Submit/Final Date:08/08/2011, COR-MEET-05(Meeting- Preliminary Comments)
[2] DARRTS: IND- (b) (4) MONTELEONE, MICHAEL V, Submit/Final Date:08/08/2011, FRM-ADMIN-31(Meeting Cancellation)

information provided.

- The FDA agrees that the pharmacokinetics (PK), efficacy and safety data in the public domain and from the approved labeling of Cardene I.V. Premixed Injection support the efficacy and safety of Exela's proposed drug products for the same indications.
- NDA 019734, not NDA 022276 (Nicardipine Hydrochloride Injection), is the application from which PK, efficacy, and safety support are to be drawn for the current pIND, although the proposed drug product is more similar to NDA 022276.
- Based on the submitted information, the application would not appear to trigger PREA.
- Decisions regarding ratings in the Orange Book are made after approval by the Orange Book staff.
- The FDA may waive the bioavailability/bioequivalence requirement for the proposed drug product per CFR 320.22(b)(1).

The Applicant identified EKR Therapeutics' Cardene I.V. (Nicardipine Hydrochloride) Premixed Injection, 0.1 mg/mL and 0.2 mg/mL, in 0.86% and 0.83% Sodium Chloride, respectively, as the previously approved drug under NDA No. 019734 for which FDA has made a finding of safety and effectiveness. Therefore, the Applicant did not submit any new clinical data in support of Exela's new drug products.

Submission: NDA 20776/S008 is a 505(b)(2) submission in which the Applicant is requesting a waiver of *in vivo* BA/BE requirements to provide in-vivo bioavailability/bioequivalence studies as per 21 CFR § 320.22(d).

Review: The Biopharmaceutics review is focused on the evaluation and approvability of the information submitted to support the biowaiver request.

The proposed drug product formulation contains the same active ingredient in the same concentration as the listed drug product. However, the listed drug product contains citric acid (anhydrous), sodium chloride, and sorbitol whereas the proposed drug product contains only sodium chloride and pH adjusters as inactive ingredients.

RECOMMENDATION:

The evidence that the different composition of Nicardipine Hydrochloride Premixed Injection compared to that of Cardene I.V. Premixed Injection does not affect the physiological disposition of the proposed drug product is lacking. Therefore, the waiver for *in-vivo* bioavailability/bioequivalence studies cannot be granted. To support the approval of the biowaiver, the Applicant should adequately address the following requests:

1. Provide justification that in the absence of sorbitol, the physiological disposition of your proposed drug product, Nicardipine Hydrochloride Premixed Injection, 0.1 mg/mL and 0.2 mg/mL, in 0.9% Sodium Chloride is not different than that of the

listed drug product, Cardene I.V. (Nicardipine Hydrochloride) Premixed Injection, 0.1 mg/mL and 0.2 mg/mL, in 0.86% and 0.83% Sodium Chloride.

2. Submit comparative physicochemical property data, such as osmolarity, of your proposed drug product and the listed drug product. The comparative data for your proposed drug product and the listed drug product should be provided using at least 3 production lots, if available, of the proposed drug product, and 3 commercial lots of the listed drug product. The measurements should be done in triplicate for each lot tested.

From the Biopharmaceutics perspective, at this time a **COMPLETE RESPONSE** (CR) is recommended for NDA 22276/S008 for Nicardipine Hydrochloride Premixed Injection, 0.1 mg/mL and 0.2 mg/mL, in 0.9% Sodium Chloride. The above request should be conveyed to the Applicant in the CR letter.

Signature	**Signature**
Kelly M. Kitchens, Ph.D.	Angelica Dorantes, Ph.D.
Biopharmaceutics Reviewer	Biopharmaceutics Team Leader
Office of New Drug Quality Assessment	Office of New Drug Quality Assessment

cc. RLostritto.

BIOPHARMACEUTICS ASSESSMENT

The finished drug product, Nicardipine Hydrochloride Premixed Injection, is supplied as is supplied as a sterile, colorless to yellow, solution with a concentration of 0.1 mg/mL or 0.2 mg/mL. (b) (4) drug product strengths are available as 200 mL solution fills in 200 mL (b) (4) Nicardipine Hydrochloride Premixed Injection, 0.1 mg/mL and 0.2 mg/mL, in 0.9% Sodium Chloride is intended for intravenous use without further dilution.

Although NDA 22276 was previously approved for Nicardipine Hydrochloride Injection, 25 mg/vial, on July 24, 2008, the Applicant is relying on the FDA safety and efficacy findings for Cardene I.V. (Nicardipine Hydrochloride) Premixed Injection, 0.1 mg/mL and 0.2 mg/mL, in 0.86% and 0.83% Sodium Chloride, respectively, to support the safety and efficacy of the proposed drug product. The Applicant provided the following comparison tables of the proposed drug product formulations to the listed drug product formulations:

Comparison of Exela's 0.1 mg/mL Drug Product with EKR Therapeutics Cardene I.V. Premixed Injection in 0.86% Sodium Chloride (0.1 mg/mL)

Ingredients	Exela's Formulation	EKR's Formulation[1]
Nicardipine Hydrochloride	0.1 mg/mL	0.1 mg/mL
Sodium Chloride, USP	9.0 mg/mL	8.6 mg/mL
Citric Acid, anhydrous, USP	(b) (4)	0.0192 mg/mL
Sorbitol, NF	(b) (4)	1.92 mg/mL
Hydrochloric Acid	pH to (b) (4)	pH to 3.7 – 4.7
Sodium Hydroxide	(b) (4)	pH to 3.7 – 4.7
(b) (4)		

[1] Information regarding EKR Therapeutics Cardene I.V. Premixed Injection in 0.86% Sodium Chloride (0.1 mg/mL) formulation was obtained from the current package insert.

Comparison of Exela's 0.2 mg/mL Drug Product with EKR Therapeutics Cardene I.V. Premixed Injection in 0.83% Sodium Chloride (0.2 mg/mL)

Ingredients	Exela's Formulation	EKR's Formulation[1]
Nicardipine Hydrochloride	0.2 mg/mL	0.2 mg/mL
Sodium Chloride, USP	9.0 mg/mL	8.3 mg/mL
Citric Acid, anhydrous, USP	(b) (4)	0.0384 mg/mL
Sorbitol, NF	(b) (4)	3.84 mg/mL
Hydrochloric Acid	pH to (b) (4)	pH to 3.7 – 4.7
Sodium Hydroxide	(b) (4)	pH to 3.7 – 4.7

[1] Information regarding EKR Therapeutics Cardene I.V. Premixed Injection in 0.86% Sodium Chloride (0.2 mg/mL) formulation was obtained from the current package insert.

- The above tables indicate that the proposed drug product formulations and the listed drug product formulations contain the same active ingredient in the same concentration. Aside from the pH adjusters, sodium chloride was the only excipient used in the proposed drug product formulations, whereas sodium chloride, citric acid and sorbitol were the excipients used in the listed drug product formulations.

Biopharmaceutics Reviewer comments:

- The proposed drug product compositions in the above tables (provided in Module 3.2.P.2.2, sections 1.3.1 and 1.3.2) are inconsistent with the proposed drug product composition described in Module 3.2.P.1 (Description and Composition), specifically the quantity of the sodium chloride ingredient:

1.1 UNIT COMPOSITION FOR NICARDIPINE HYDROCHLORIDE PREMIXED INJECTION

Component	Quality Standard	Function	Nicardipine Hydrochloride Premixed Injection (0.1 mg / mL and 0.2 mg / mL)
Nicardipine Hydrochloride	N/A	Drug Substance	0.1 mg / mL and 0.2 mg / mL
Sodium Chloride	USP	(b) (4)	(b) (4) mg/mL
Hydrochloric Acid	USP	pH adjuster	pH to (b) (4)
(b) (4)			

- The Applicant did not provide justification that in the absence of citric acid and sorbitol, the physiological disposition of the proposed drug product is not different than that of the listed drug product.

- The Applicant did not submit comparative physicochemical property data for the proposed drug product and the listed drug product.

RECOMMENDATION:

The evidence that the different composition of Nicardipine Hydrochloride Premixed Injection compared to that of Cardene I.V. Premixed Injection does not affect the physiological disposition of the proposed drug product is lacking. Therefore, the waiver for *in-vivo* bioavailability/bioequivalence studies cannot be granted. To support the approval of the biowaiver, the Applicant should adequately address the following requests:

1. Provide justification that in the absence of sorbitol, the physiological disposition of your proposed drug product, Nicardipine Hydrochloride Premixed Injection, 0.1 mg/mL and 0.2 mg/mL, in 0.9% Sodium Chloride is not different than that of the listed drug product, Cardene I.V. (Nicardipine Hydrochloride) Premixed Injection, 0.1 mg/mL and 0.2 mg/mL, in 0.86% and 0.83% Sodium Chloride.

2. Submit comparative physicochemical property data, such as osmolarity, of your proposed drug product and the listed drug product. The comparative data for your proposed drug product and the listed drug product should be provided using at least 3 production lots, if available, of the proposed drug product, and 3 commercial lots of the listed drug product. The measurements should be done in triplicate for each lot tested.

From the Biopharmaceutics perspective, at this time a **COMPLETE RESPONSE** (CR) is recommended for NDA 22276/S008 for Nicardipine Hydrochloride Premixed Injection, 0.1 mg/mL and 0.2 mg/mL, in 0.9% Sodium Chloride. The above request should be conveyed to the Applicant in the CR letter.

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/s/

KELLY M KITCHENS
07/12/2013

ANGELICA DORANTES
07/12/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022276Orig1s008

OTHER REVIEW(S)

DIVISION OF CARDIOVASCULAR & RENAL PRODUCTS

Regulatory Project Manager Review

NDA:	22276/S-008
Drug:	Nicardipine Hydrochloride 0.1mg/mL and 0.2mg/mL Injection
Applicant:	Exela Pharma Sciences, LLC
Submission date:	December 07, 2015
RPM Review date:	April 06, 2016
Reviewers:	Kris Raman, Denise Miller, Thomas Papoian, Janine Stewart, Mary Ann Holovac, and Michael Monteleone

Background and summary of description

This CMC supplement was originally received on March 29, 2013 pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. It proposed new premixed formulations of Nicardipine Hydrochloride 0.1mg/mL and 0.2mg/mL in 0.9% Sodium Chloride.

The Applicant received a Complete Response on July 25, 2013 as several product quality deficiencies were identified. In addition, the submission lacked the appropriate patent certification.

On December 07, 2015, the Applicant submitted a formal response to our Complete Response addressing the deficiencies and the additional recommendations that were not approvability issues.

REVIEW

Product quality

Dr. Raman completed a review and noted that all CMC responses were complete and adequate.
Dr. Miller reviewed the sterility information and concluded that they were no concerns.

Non-clinical

Dr. Papoian reviewed the container closure extractable and leachable data. He concluded that there were no safety concerns from a pharmacology or toxicology perspective.

Labeling

Dr. Stewart reviewed the revised container labels (premixed bag labels), carton labeling

(overwrap), and Prescribing Information for areas of vulnerability that could lead to medication errors. Her comments were conveyed to the Division and to the Applicant.

Patent

The 505(b)(2) committee reviewed this application on March 14, 2016 and cleared it for action.

Recommendations

The review team agreed that this supplement can be approved. An approval letter will be generated and sent to Dr. Stockbridge for review and approval.

Attachments:

E-mail from Mr. Sterling agreeing to the changes made by the Division

From: Jonathan Sterling
To: Soukehal, Sabry
Subject: Re: NDA 22276 s008
Date: Tuesday, April 05, 2016 8:22:00 PM

Ok. Please approve without this addition.

We will file final labeling upon receipt of the approval letter.

On Apr 5, 2016, at 7:21 PM, Soukehal, Sabry <Sabry.Soukehal@fda.hhs.gov> wrote:

> Thank you for the timely response.
>
> ---
>
> **From:** Jonathan Sterling [mailto:jsterling@exela.us]
> **Sent:** Tuesday, April 05, 2016 7:19 PM
> **To:** Soukehal, Sabry
> **Subject:** Re: NDA 22276 s008
>
> Fine. We will remove it.
>
> On Apr 5, 2016, at 7:08 PM, Soukehal, Sabry <Sabry.Soukehal@fda.hhs.gov> wrote:
>
> > I'm not exactly sure why. However, to finish this supplement on time, and if you are OK with it, can we proceed with the label without the added warning? We can perhaps have a side discussion independent of this supplement.
> >
> > ---
> >
> > **From:** Jonathan Sterling [mailto:jsterling@exela.us]
> > **Sent:** Tuesday, April 05, 2016 6:00 PM
> > **To:** Soukehal, Sabry
> > **Subject:** Re: NDA 22276 s008
> >
> > What is the reservation with the additional warning. If it is going to cause delay I agree to remove it
> >
> > On Apr 5, 2016, at 3:57 PM, Soukehal, Sabry <Sabry.Soukehal@fda.hhs.gov> wrote:
> >
> > > Jonathan,
> > >
> > > I need a response as soon as possible as the due date it April 7th.
> > >
> > > Happy to talk if necessary.

Thank you,
Sabry

From: Soukehal, Sabry
Sent: Monday, April 04, 2016 11:35 PM
To: 'Jonathan Sterling'
Subject: RE: NDA 22276 s008

Jonathan,

Our team reviewed your proposed change in section 2.2 (addition of (b) (4) and concluded that it was not necessary.
Do we have your agreement that the PI can be finalized without the added sentence?

Thank you,
Sabry

From: Jonathan Sterling [mailto:jsterling@exela.us]
Sent: Friday, April 01, 2016 7:43 PM
To: Soukehal, Sabry
Subject: RE: NDA 22276 s008

Please see attached. I accepted all changes and proposed a few minor edits as tracked in the changes copy. The tracked changes copy also contains Exela's response to all FDA comments.

The clean copy incorporates all of the Divisions requests and Exela's proposed revisions.

Formal filing to the submission will be completed today.

Also, see IR response attached concerning the (b) (4) to bag calculation.

JES

From: Soukehal, Sabry [mailto:Sabry.Soukehal@fda.hhs.gov]
Sent: Friday, April 01, 2016 9:42 AM
To: Jonathan Sterling
Subject: RE: NDA 22276 s008

Jonathan,

Thank you for the update. In addition to the comments you received, our CMC group has one additional comment:

in the **How Supplied** section the following should be added (shown in bold red):

NDC	Strength	Packaged
0143-9634-01	20 mg in 200 mL (0.1 mg/mL)	**Flexible Containers**
0143-9633-01	40 mg in 200 mL (0.2 mg/mL)	**Flexible Containers**

Could you please confirm that it is acceptable?

Thank you,
Sabry

From: Jonathan Sterling [mailto:jsterling@exela.us]
Sent: Friday, April 01, 2016 9:00 AM
To: Soukehal, Sabry
Subject: RE: NDA 22276 s008

I have no changes to be made.

I will accept all changes and provide a clean sponsor accepted copy to the filing.

From: Soukehal, Sabry [mailto:Sabry.Soukehal@fda.hhs.gov]
Sent: Thursday, March 31, 2016 12:15 PM
To: Jonathan Sterling
Subject: NDA 22276 s008
Importance: High

Jonathan,

Attached please find our comments on the PI.

Because of the due date (April 7th) and my team's availability next week, please let me know **no later than**

tomorrow, April 1st if your team accepts the changes or if they have any comments.

I'd also like to follow up on my previous request (documentation for the information regarding the number of bags represented by 25 gms of test material). We'll also need this information no later than tomorrow to complete and clear our reviews on time.

I am offsite today and tomorrow. The best way to reach me is by email but I can get on the phone if needed.

Thank you,

Sabry Soukehal
Regulatory Health Project Manager
Division of Cardiovascular and Renal Products
Center for Drug Evaluation and Research
Food and Drug Administration
sabry.soukehal@fda.hhs.gov
p: (240) 402 6187
f:(301) 796-9838

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/s/

SABRY SOUKEHAL
04/07/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 21, 2016
Requesting Office or Division:	Office of Program and Regulatory Operations (OPRO)
Application Type and Number:	NDA 022276/S-008
Product Name and Strength:	Nicardipine Hydrochloride in 0.9% Sodium Chloride Injection 20 mg in 200 mL (0.1 mg/mL) 40 mg in 200 mL (0.2 mg/mL)
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Exela Pharma Sciences
Submission Date:	December 4, 2015
OSE RCM #:	20016-615
DMEPA Primary Reviewer:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

This review evaluates the revised container labels (premixed bag labels), carton labeling (overwrap), and Prescribing Information for Nicardipine Hydrochloride in 0.9% Saline Injection (NDA 022276/S-008) for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

Supplement 008 to NDA 022276 was originally submitted on March 27, 2013. The Supplement proposed new premixed formulations; Nicardipine Hydrochloride in 0.9% sodium chloride Injection, 20 mg in 200 mL (0.1 mg/mL) and 40 mg in 200 mL (0.2 mg/mL). After Agency review, a Complete Response (CR) was issued on July 25, 2013. The action included labels and labeling deficiencies identified by DMEPA and our recommendations. On December 4, 2015, the Applicant submitted a formal response to the CR. The Applicant has resubmitted labels and labeling to address DMEPA's prior recommendations. OPRO requested DMEPA's review of the resubmitted labels and labeling.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C- N/A
ISMP Newsletters	D- N/A
FDA Adverse Event Reporting System (FAERS)*	E- N/A
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA performed a risk assessment of the revised container labels (premixed bag labels), carton labeling (overwrap), and Prescribing Information (PI) to identify deficiencies that may lead to medication errors and areas for improvement.

Based on our previous review and the formal response from the Applicant, we found that our previous recommendations were not completely implemented. We note that the recommendations with regard to the PI were not applied to the sections within the Highlights of Prescribing Information which correspond to the revised sections of the Full Prescribing Information. We also note that important product information does not appear on the revised container labels.

Therefore, we provide recommendations in Section 4 in order to promote the safe use of this product.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed Nicardipine Hydrochloride in 0.9% sodium chloride Injection labels and labeling can be improved to increase clarity, readability, and the prominence of important information to promote the safe use of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

Based on this review, we recommend revisions to the proposed Prescribing Information (PI) for review and consideration by DCRP. See Appendix G for tracked change edits to the proposed PI.

4.2 RECOMMENDATIONS FOR EXELA PHARMA SCIENCES

We recommend the following be implemented prior to approval of this NDA Supplement:

A. General Comments

1. The similarity of the NDC product code numbers (middle 3-4 digits) has led to selecting and dispensing of the wrong strength and wrong drug. The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. The assignment of sequential numbers for the middle digits is not an effective differentiating feature (e.g., 9633 and 9634). Therefore, revise the product codes to provide greater differentiation between the NDC numbers of the two strengths.

B. Container Labels

1. Ensure the lot number and expiration date are present on the container labels (premixed bag labels).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Nicardipine Hydrochloride that Exela Pharma Sciences submitted on December 4, 2015, and the listed drug (LD).

Table 2. Relevant Product Information for Nicardipine Hydrochloride and the Listed Drug

Product Name	**Nicardipine Hydrochloride**	**Cardene** (NDA 019734)
Initial Approval Date	July 24, 2008	January 30, 1992
Active Ingredient	nicardipine hydrochloride	nicardipine hydrochloride
Indication	For the short-term treatment of hypertension when oral therapy is not feasible.	For the short-term treatment of hypertension when oral therapy is not feasible or not desired.
Route of Administration	Intravenous	Intravenous
Dosage Form	Solution for Injection Pre-mixed Solution (proposed)	Solution for Injection Pre-mixed Solution
Strength	25 mg/10 mL ampules Proposed: 20 mg in 200 mL (0.1 mg/mL) 40 mg in 200 mL (0.2 mg/mL)	25 mg/10 mL vials 20 mg in 200 mL (0.1 mg/mL)
Dose and Frequency	Initiate therapy at 50 mL/hr (5 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 mg/hr), until desired blood pressure reduction is achieved. If unacceptable hypotension or tachycardia ensues, discontinue the infusion. When blood pressure and heart rate stabilize, restart the infusion at low doses such as 30 mL/hr to 50 mL/hr (2.5).	Initiate therapy at 50 mL/hr (5 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 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).

How Supplied	• Cartons of 10- 10 mL ampules • 10 bags, each containing 20 mg in 200 mL (0.1 mg/mL) or 40 mg in 200 mL (0.2 mg/mL) nicardipine hydrochloride in sodium chloride	• Cartons of 10- 10 mL vials • 10 bags, each containing 20 mg in 200 mL (0.1 mg/mL) nicardipine hydrochloride in either dextrose or sodium chloride
Storage	Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Freezing does not adversely affect the product, but exposure to elevated temperatures should be avoided. Protect from light. Store vials in carton until used.	Store at controlled room temperature 20º to 25ºC (68º to 77ºF), refer to USP Controlled Room Temperature. Protect from freezing. Avoid excessive heat. Protect from light, store in carton until ready to use.
Container Closure	Premixed bag is made of (b) (4) The overwrap material is solid (like an aluminum foil material).	200 mL GALAXY container (premixed bag)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On March 15, 2016 we searched the L: drive and AIMS using the terms, Nicardipine to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one (1) previous review that is relevant to this review.[1]

[1] DeFronzo, K. Labeling and Labeling Review for Nicardipine NDA 022276. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 JUL 23. RCM No.: 2013-1496.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[2] along with postmarket medication error data, we reviewed the following Nicardipine Hydrochloride labels and labeling submitted by Exela Pharma Sciences on December 4, 2015.

- Container labels (premixed bag labels)
- Carton Labeling (Overwrap)
- Prescribing Information

G.2 Label and Labeling Images

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[2] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JANINE A STEWART
03/21/2016

CHI-MING TU
03/21/2016

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	July 23, 2013
Reviewer:	Kimberly DeFronzo, RPh, MS, MBA Division of Medication Error Prevention and Analysis
Associate Director:	Scott Dallas, RPh Division of Medication Error Prevention and Analysis
Drug Name(s) and Strength:	Nicardipine Hydrochloride in 0.9% Sodium Chloride Solution 20 mg in 200 mL (0.1 mg/mL) Flexi-Bag 40 mg in 200 mL (0.2 mg/mL) Flexi-Bag
Application Type/Number:	NDA 22276
Supplement Number:	008
Applicant:	Exela Pharma Sciences
OSE RCM #:	2013-1496

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Contents

1 INTRODUCTION

This review evaluates the proposed premixed bag (inner) label, overwrap (outer) labeling, and insert labeling for Nicardipine Hydrochloride in 0.9% Saline Solution (NDA 22276) for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND AND REGULATORY HISTORY

Nicardipine Hydrochloride Injection 25 mg per vial was approved on July 24, 2008. Nicardipine Hydrochloride Injection must be diluted prior to administration. The current approved labeling provides directions to prepare a Nicardipine Hydrochloride Solution for intravenous infusion with a concentration of 0.1 mg/mL. This supplement requests approval of two proposed "ready to use" dosage formulations, Nicardipine Hydrochloride Premixed Injection in 0.9% Sodium Chloride to be supplied as 200 mL Flexi-Bag in concentrations of 0.1 mg/mL and 0.2 mg/mL.

1.2 PRODUCT INFORMATION

The following product information is provided in the March 29, 2013 submission.

- Active Ingredient: Nicardipine Hydrochloride
- Indication of Use: For the short-term treatment of hypertension when oral therapy is not feasible
- Route of Administration: Intravenous
- Dosage Form: Pre-mixed Solution
- Strength: 20 mg in 200 mL (0.1 mg/mL) or 40 mg in 200 mL (0.2 mg/mL)
- Dose and Frequency: (proposed)
    - In a drug-free patient, initiate therapy at (b) (4) (5 mg/hr). (b) (4) increase the infusion rate by (b) (4) to a maximum of (b) (4) until desired blood pressure reduction is achieved. (b) (4) blood pressure reduction, (b) (4) the (b) (4) rate (b) (4) (2.4). If (b) (4) hypotension or tachycardia ensues, discontinue the infusion. (b) (4) restart (b) (4) at low doses such as (b) (4) /hr to (b) (4) /hr (2.5).
- How Supplied: Nicardipine Hydrochloride in 0.9% (b) (4) Solution is available in packages as follows:

NDC	Strength
0143-9634-01	0.1 mg/mL in 200 mL flexible containers
0143-9633-01	0.2 mg/mL in 200 mL flexible containers

- Storage: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Freezing does not adversely affect the product, but exposure to elevated temperatures should be avoided. Protect from light. Store vials in carton until used.
- Container and Closure System: Premixed bag is made of " (b) (4) The overwrap material is solid (like an aluminum foil material). See Appendix F for a picture of the container and closure system.

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for either Nicardipine or Cardene medication error reports relating to the premixed bag formulation (See Appendix A for a description of the FAERS database). We also reviewed the Nicardipine labels and labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS database using the strategy listed in Table 1 below.

Table 1: FAERS Search Strategy

Date	Conducted 6/28/2013 and was limited from January 30, 1992 to present (since January 30, 1992 was the approval date of the Cardene premixed bags)
Drug Names	(Active Ingredient) Nicardipine (Product Name) Cardene (Product Verbatim) Cardene
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The FAERS database search identified 24 cases. Each case was reviewed for relevancy and duplication. After individual review, 21 cases were not included in the final analysis for the following reasons:

- Name confusion due to sound-alike or look-alike to Cardizem or Cordarone
- Suicide/Overdose
- Medication error relating to the capsule or vial (not with the intravenous infusion bag)

2.2 LITERATURE SEARCH

We searched PubMed on June 28, 2013 for additional cases and actions concerning Cardene or nicardipine premixed formulation. No cases were found.

2.3 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Bag Labels submitted March 29, 2013 (Appendix B)
- Overwrap Labeling submitted March 29, 2013 (Appendix C)
- Insert Labeling submitted March 29, 2013

2.4 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed labels and labeling for Nicardipine 25 mg per 10 mL vials under OSE RCM #2011-2397 and 2011-4085. However, we did not previously review the premixed bag labels or labeling for Cardene or Nicardipine Premixed Solution.

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of the proposed Nicardipine product design as well as the associated label and labeling.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, there were 3 Cardene medication error cases remained for our detailed analysis. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter[2]. Appendix G provides listings of all case numbers for the cases discussed in this review.

The first case (#7144851 v.1) reported the Cardene I.V. premixed injection in dextrose contained labeling identical to that of the Cardene I.V. product premixed in sodium chloride. The reporter noted that while an adverse event has not yet occurred, the confusing labeling may leave the door open for the wrong medication to be pulled and dispensed. A review of the Cardene bag labels for these products (see Appendix D) in both dextrose and sodium chloride confirmed the similarities noted by the reporter. However, the nicardipine premixed bags proposed by the Applicant will only be available in one diluent, in sodium chloride. Therefore, the potential for confusion that existed with the Cardene premixed product line is not expected to occur with this proposed premixed product.

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[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

[2] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www nccmerp.org/pdf/taxo2001-07-31.pdf. Accessed June 1, 2011.

The remaining two cases (#8806480 v.1 received 9/18/12, and #8986743 v.1 received 12/19/12) reported the same error type of label similarity between the premixed Amiodarone (Nexterone) and the premixed Nicardipine (Cardene) infusions. One case reported that "the Nexterone product looked extremely similar to the premixed Cardene infusions that we already use". The other case reported "the possibility of a look-alike error occurring between pre-mixed Amiodarone (Nexterone) and Nicardipine (Cardene)". The narratives noted that both cases were potential medication errors without patient involvement. However, the narratives did not specify whether the similarities involved the inner bag labels or the outer overwrap labeling.

Upon examining the current bag labels and carton labeling of Cardene and Nexterone, we note there are similarities between the bag labels (b) (4) (b) (4) However, we noted sufficient differentiation between the carton labeling for these two products. Please see Appendices D through F for labels and labeling of these products. Due to these observations, we will make a recommendation for the proposed product to (b) (4) (b) (4)

3.2 Integrated Summary of Medication Error Risk Assesment

An analysis of the FAERS cases identified revealed a potential for confusion with the currently marketed premixed formulations of Cardene and Nexterone due to similarities of (b) (4) . Therefore, the proposed bag labels should avoid (b) (4) to minimize confusion with these two products in the marketplace.

Furthermore, we noted minimal differentiation between the two proposed Nicardipine bag labels (b) (4) Therefore, we contacted the Applicant to inquire about the feasibility of using unique color schemes for each strength to help increase product differentiation. On July 1, 2013, the Applicant responded to our Information Request via email confirming that the "bag supplier is not able to mix colors, or use color blocks; however, it is possible to use one solid other color". Therefore, we will provide a recommendation to the Applicant to use a different unique color scheme (e.g., blue) to help further differentiate the two strengths and minimize product confusion between the proposed product with Cardene and Nexterone.

Due to the different concentrations being proposed by the Applicant, we also noted the error-prone expression of the infusion rate by a volume amount per hour (i.e., mL/hr). We recommend avoiding this practice since this designation will result in inaccurate amounts of drug being infused since the final drug amount will vary depending on the concentration of the premixed bag being administered. Therefore, we will provide recommendation under section 5 to replace the (b) (4) with the "mg/hr" expression to avoid wrong dose medication errors.

4 CONCLUSIONS

DMEPA concludes that the proposed label and labeling can be improved to mitigate confusion and dosing errors.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this supplement:

A. Comments to the Division

1. Revise the statement [redacted] (b) (4)" found throughout the insert labeling with the USP recognized terminology of "0.9% Sodium Chloride Injection".
2. Delete the [redacted] (b) (4)" reference as an expression for the infusion rate (in the Dosage and Administration section 2.4 Dosage for Initiation of Therapy in a Drug-Free Patient, Subsection Titration) and only present the infusion rate referencing the "mg/hr" for the total amount of drug intended per hour. The [redacted] (b) (4) will be dependent upon the concentration selected and there are two concentrations being proposed for this supplement.
3. Under the Dosage Forms and Strengths section 3 of the insert labeling, we recommend revising the strength statement from "20 mg (0.1 mg/mL)" and "40 mg (0.2 mg/mL)" to read "20 mg in 200 mL (0.1 mg/mL)" and "40 mg in 200 mL (0.2 mg/mL)", respectively.
4. Similarly, under the How Supplied/Storage and Handling section 16.1 of the insert labeling, we recommend revising the strength statement from "0.1 mg/mL in 200 mL…" and "0.2 mg/mL in 200 mL…" to read "20 mg in 200 mL (0.1 mg/mL)" and "40 mg in 200 mL (0.2 mg/mL)", respectively.
5. To improve clarity of the storage condition statement under the How Supplied/Storage and Handling section 16.2 of the insert labeling, we recommend adding the units of measure after the temperature. For example, revise "20°" to read "20°C" and "68°" to read "68°C".

B. Comments to the Applicant

Bag (inner) Label

1. Consider increasing the differentiation between the two strengths by using a different color scheme for one of the strengths (e.g., blue color for the 0.1 mg/mL strength). The blue color would help differentiate the lower strength (0.1 mg/mL) from the black color used on the label for the higher strength (0.2 mg/mL).
2. Revise the statement [redacted] (b) (4)" found under the product name with the USP recognized terminology of "0.9% Sodium Chloride Injection".
3. The route of administration is absent. Therefore, we recommend adding the route of administration statement "For Intravenous Infusion".
4. Below the statement, "Single Dose Container", add the statement "Discard Unused Portion" to reinforce to the user that the contents of the bag should be discarded after retrieving the required dose.

5. Increase the font size of the strength expressions (e.g., 20 mg in 200 mL and 0.1 mg/mL), and revise the strength statements to appear in a stacked format. For example:

20 mg in 200 mL
(0.1 mg/mL)

6. Revise the established name such that it includes mixed case letters (e.g., "Nicardipine Hydrochloride").
7. Ensure the lot and expiration date is present on the label as it appears to be missing.
8. Minimize the prominence of the distributor name, West-Ward, to avoid competing with other important information on this crowded label.

Overwrap Labeling

1. See 1 through 6 above.
2. If possible, increase the overall size of the label to improve readability of all the information presented on the labeling.
3. Remove the [redacted] (b) (4) and avoid the use of the [redacted] (b) (4) for the lower strength of 20 mg in 200 mL (0.1 mg/mL) to reduce potential for confusion with the same proposed [redacted] (b) (4) scheme on the 40 mg in 200 mL (0.2 mg/mL). In addition, we note the removal of the [redacted] (b) (4) [redacted] (b) (4) scheme may further help differentiate the proposed (0.1 mg/mL) strength [redacted] (b) (4)

If you have further questions or need clarifications, please contact Cherye Milburn, OSE Project Manager, at 301-796-2084.

APPENDICES

Appendix A. Database Descriptions

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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/s/

KIMBERLY A DE FRONZO
07/23/2013

SCOTT M DALLAS
07/23/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022276Orig1s008

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

505(b)(2) ASSESSMENT

Application Information		
NDA # 22276	NDA Supplement #: S- 008	Efficacy Supplement Type SE- n/a (CMC)
Proprietary Name: n/a Established/Proper Name: nicardipine hydrochloride Dosage Form: premixed injection Strengths: 0.1 mg/mL and 0.2 mg/mL		
Applicant: Exela Pharma Sciences, LLC		
Date of (resubmission) Receipt: December 07, 2015		
PDUFA Goal Date: April 07, 2016	Action Goal Date (if different):	
RPM: Sabry Soukehal		
Proposed Indication(s): Short-term treatment of hypertension when oral therapy is not feasible		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 19734 (Cardene)	FDA's previous finding of safety and effectiveness

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

The original application (NDA 22276) was granted a waiver from the requirement for in vivo BA/BE studies.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
CARDENE (nicardipine)	19734	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☐ YES ☒ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

New Formulation – benzoic acid replacing citric acid monohydrate as the (b) (4) agent and sodium chloride replacing sorbitol as the (b) (4) agent.
Additionally, this supplemental application proposes two new pre-mixed bag formulations.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☒ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*

*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s): NDA 20005 (Cardene SR, ER Capsules), NDA 19488 (Cardene Capsules), generic capsules, and generic injectables.

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 7,612,102; 7,659,291; 8,455,524

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 7,612,102; 7,659,291; 8,455,524

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): June 11, 2013

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☒ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

APPEARS THIS WAY ON ORIGINAL

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/s/

SABRY SOUKEHAL
04/05/2016

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Darrell Lyons & Tri Minh Bui-Nguyen
OMPT/CDER/OSE/PMS
Mail: OSE

FROM: Yvonne Knight, OPRO, (301) 796-2133

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
3/14/16		22276	S-008	12/4/15

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Nicardipine Hydrochloride Premixed Injection	PAS (Resubmission)		**3/21/16 per DCRP (per Norman Stockbridge)**

NAME OF FIRM: Exela Pharma Sciences, LLC

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
- ☐ 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:

The supplement proposes new premixed formulations, Nicardipine Hydrochloride Premixed Injection, 0.1 mg/mL and 0.2 mg/mL, in 0.9% sodium chloride. The applicant resubmitted labeling to address DMEPA's prior comments.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check all that apply)
Yvonne Knight	☐ MAIL x DARRTS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

06/18/2013

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/s/

YVONNE L KNIGHT
03/14/2016

From: Knight, Yvonne
To: Jonathan Sterling (jsterling@galexe.us)
Cc: Monteleone, Michael V.
Subject: NDA22276/S-0-08 Information Request (Additional Micro Questions)
Date: Wednesday, July 10, 2013 11:25:00 AM

Good morning Jonathan,

We have the following information request concerning your supplemental New Drug Application (sNDA) for NDA 22276/S-008.

Please provide the following information by COB July 15, 2013.

Microbiology Information Request:

We acknowledge your response to our 19 June 2013 Product Quality Microbiology information request. More information is needed. Address the following points.

1. [redacted] (b) (4) ?
2. [redacted] (b) (4)
3. Your drug product release specifications call for an endotoxin limit of (b) (4) EU/mg, while your stability specifications call for an endotoxin limit of (b) (4) EU/mg. Provide a justification for this difference in endotoxin specifications.

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official response? If you have any questions or comments feel free to contact me.

Best Regards,

Yvonne Knight, MS
Regulatory Health Project Manager

Division of New Drug Quality Assessment
FDA/CDER/OPS/ONDQA
Phone (301) 796 – 2133
Fax: (301) 796 – 9749

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/s/

YVONNE L KNIGHT
07/10/2013

From:	Knight, Yvonne
To:	Jonathan Sterling (jsterling@galexe.us)
Cc:	Monteleone, Michael V.
Subject:	NDA 22276/S-008 Information Request
Date:	Friday, July 05, 2013 4:46:00 PM

Good afternoon Jonathan,

We have the following information request concerning your supplemental New Drug Application (sNDA) for NDA 22276/S-008.

Please provide the following information by COB July 22, 2013.

Biopharm Reviewer Information Request:

1. Provide justification that in the absence of sorbitol, the physiological disposition of your proposed drug product, Nicardipine Hydrochloride Premixed Injection, 0.1 mg/mL and 0.2 mg/mL, in 0.9% Sodium Chloride is not different than that of the listed drug product, Cardene I.V. (Nicardipine Hydrochloride) Premixed Injection, 0.1 mg/mL and 0.2 mg/mL, in 0.86% and 0.83% Sodium Chloride.

2. Submit comparative physicochemical property data, such as osmolarity, of your proposed drug product and the listed drug product. The comparative data for your proposed drug product and the listed drug product should be provided using at least 3 production lots, if available, of the proposed drug product, and 3 commercial lots of the listed drug product. The measurements should be done in triplicate for each lot tested.

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official response? If you have any questions or comments feel free to contact me.

Best Regards,

Yvonne Knight, MS
Regulatory Health Project Manager
Division of New Drug Quality Assessment
FDA/CDER/OPS/ONDQA
Phone (301) 796 – 2133

Fax: (301) 796 – 9749

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/s/

YVONNE L KNIGHT
07/05/2013

From: Knight, Yvonne
To: Jonathan Sterling (jsterling@galexe.us)
Cc: Knight, Yvonne
Subject: NDA 22276/S-008
Date: Thursday, June 27, 2013 3:45:00 PM

Good afternoon Jonathan,

We have the following information request concerning your supplemental New Drug Application (sNDA) for NDA 22276/S-008.

Please provide the following information by COB July 11, 2013.

Product Quality Reviewer Information Request:

1. Please provide a list of all establishments for drug substance and drug product manufacturing and release, stability testing and packaging. Clarify if any new establishments involve this supplement for the proposed strengths of 0.1 mg/mL and 0.2 mg/mL. The information provided in M1 under file "Establishment Information" does not corroborate with the information in M3 for both Drug Substance and Drug Product sections for sites involved in manufacturing, release, stability testing and packaging.

2. Clarify for all sections of Drug Substance and Drug Product, the differences between the approved 2.5 mg/mL formulation and the proposed 0.1 mg/mL and 0.2 mg/mL. Include information related to composition, manufacturing sites, release and stability specifications, container closure system and stability data to support expiration dating. The information can be provided in a tabular format with hyperlinks for different sections to delineate any differences.

3. Are stability studies performed using the proposed commercial container closure? Please provide details.

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official response? If you have any questions or comments feel free to contact me.

Best Regards,

Yvonne Knight, MS
Regulatory Health Project Manager
Divison of New Drug Quality Assessment
FDA/CDER/OPS/ONDQA
Phone (301) 796 – 2133
Fax: (301) 796 – 9749

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/s/

YVONNE L KNIGHT
06/27/2013

From: Knight, Yvonne
To: "jsterling@galexe.us"
Subject: NDA 22276/S-008 Information Request
Date: Wednesday, June 19, 2013 11:11:00 AM

Good morning Jonathan,

We have the following information request concerning your supplemental New Drug Application (sNDA) for NDA 22276/S-008.

Please provide the following information by COB July 2, 2013.

Microbiology Information Request:

1. You state that sterilization of the drug product [redacted] (b) (4) [redacted] Describe methods and controls to manage sterilization [redacted] (b) (4) during production.
2. [redacted] (b) (4)
3. You state that [redacted] (b) (4) used in sterilization validation studies [redacted] (b) (4) according to manufacturer's instructions [redacted] (b) (4) Describe the [redacted] (b) (4) [redacted] (b) (4) and the length and temperature of incubation periods.

Please contact me if you have any questions or comments.

Best Regards,

Yvonne Knight, MS
Regulatory Health Project Manager
Division of New Drug Quality Assessment
FDA/CDER/OPS/ONDQA
Phone (301) 796 – 2133
Fax: (301) 796 – 9749

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/s/

YVONNE L KNIGHT
06/19/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 22-276/S-008

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

Exela Pharma Sciences, LLC
Attention: Jonathan E. Sterling
Vice President of Quality, Regulatory & Product Development
1325 William White Place
PO Box 818
Lenoir, NC 28645

Dear Mr. Sterling:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505 (b) of the Federal Food, Drug and Cosmetic Act (FDCA or the Act) for the following:

Name of Drug Product: Cardene® (nicardipine hydrochloride premixed injection)

NDA Number: 22276

Supplement number: 008

Date of Supplement: March 27, 2013

Date of Receipt: March 29, 2013

This 'Prior Approval' supplemental application proposes two new premixed solution formulations, Nicardipine Hydrochloride Premixed Injection, 0.1 mg/mL and 0.2 mg/mL, in 0.9% sodium chloride.

We filed the application on May 28 2013, in accordance with 21 CFR 314.101(a). The user fee goal date will be July 29, 2013.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

SUBMISSION REQUIREMENTS

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-Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm

If you have questions please feel free to call me at (301) 796-2133

Sincerely,

{See appended electronic signature page}

Yvonne Knight, MS
Regulatory Health Project Manager
Division of New Drug Quality Assessment I
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

YVONNE L KNIGHT
06/10/2013

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

CMC MICRO & STERILITY ASSURANCE REVIEW REQUEST

TO *(Division/Office)*: **New Drug Microbiology Staff**

E-mail to: **CDER OPS IO MICRO**

Paper mail to: **WO Bldg 51, Room 4193**

FROM: Yvonne Knight, ONDQA, Division of New Drug Quality Assessment I (301) 796-2133

PROJECT MANAGER *(if other than sender):*

REQUEST DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
06/7/2013		022276	Supplement	04/10/2013

NAMES OF DRUG	PRIORITY CONSIDERATION	PDUFA DATE	DESIRED COMPLETION DATE
NICARDIPINE HYDROCHLORIDE INJECTION	PAS	07/29/2013	06/29/2013

NAME OF APPLICANT OR SPONSOR: Exela Pharma Sciences

GENERAL PROVISIONS IN APPLICATION

- ☐ 30-DAY SAFETY REVIEW NEEDED
- ☐ NDA FILING REVIEW NEEDED BY: _____
- ☐ BUNDLED
- ☐ DOCUMENT IN EDR
- ☐ CBE-0 SUPPLEMENT
- ☐ CBE-30 SUPPLEMENT
- ☐ CHANGE IN DOSAGE, STRENGTH / POTENCY

COMMENTS / SPECIAL INSTRUCTIONS:

Proposes two new premixed solution formulations, Nicardipine Hydrochloride Premixed Injection, 0.1 mg/mL and 0.2 mg/mL, in 0.9% sodium chloride.

SIGNATURE OF REQUESTER

REVIEW REQUEST DELIVERED BY (Check one):

☐ DARRTS ☐ EDR ☐ E-MAIL ☐ MAIL ☐ HAND

DOCUMENTS FOR REVIEW DELIVERED BY (Check one):

☐ EDR ☐ E-MAIL ☐ MAIL ☐ HAND

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/s/

YVONNE L KNIGHT
06/07/2013

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/s/

LEORA F DUGGAN
05/10/2013