



NDA 022276/S-011

SUPPLEMENT APPROVAL

Exela Pharma Sciences, LLC
Attention: Jonathon E. Sterling
Vice President, Quality, Regulatory, and Product Development
1325 William White Place
P.O. Box 818
Lenoir, SC 28645

Dear Mr. Sterling:

Please refer to your Supplemental New Drug Application (sNDA) dated September 21, 2016 and received September 23, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nicardipine Hydrochloride 2.5 mg/mL for Injection.

We also refer to our letter dated July 18, 2016, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Nicardipine Hydrochloride 2.5 mg/mL for Injection. This information pertains to the risk of a drug-drug interaction that could result in elevated levels of tacrolimus if the drugs are co-administered.

We further refer to our Safety Labeling Change Order Letter dated, September 7, 2016.

This supplemental new drug application provides for revisions to the labeling for Nicardipine Hydrochloride, consistent with our July 18, 2016 Safety Notification Letter.

1. In **HIGHLIGHTS/DRUG INTERACTIONS**, the following text was added/deleted to/from the second bullet:

Nicardipine may increase cyclosporine and tacrolimus plasma levels. Frequent monitoring of trough blood levels of cyclosporine and tacrolimus is recommended when co-administering nicardipine. (7.5, 7.6).

2. Under **DRUG INTERACTIONS**, the following text was added:

7.5 Cyclosporine

Concomitant administration of oral or intravenous nicardipine and cyclosporine results in elevated plasma cyclosporine levels through nicardipine inhibition of hepatic microsomal enzymes, including CYP3A4. Closely monitor plasma

concentrations of cyclosporine during Cardene I.V. Premixed Injection administration, and reduce the dose of cyclosporine accordingly.

7.6 Tacrolimus

Concomitant administration of intravenous nicardipine and tacrolimus may result in elevated plasma tacrolimus levels through nicardipine inhibition of hepatic microsomal enzymes, including CYP3A4. Closely monitor plasma concentrations of tacrolimus during nicardipine hydrochloride injection administration, and adjust the dose of tacrolimus accordingly.

3. Under **PHARMACOKINETICS/Metabolism and Excretion**, the following text was added/deleted:

Cardene I.V. has been shown to be rapidly and extensively metabolized by the liver. hepatic cytochrome P450 enzymes, CYP2C8, 2D6, and 3A4. Nicardipine does not induce or inhibit its own metabolism and does not induce or inhibit hepatic microsomal enzymes, however, nicardipine has been shown to inhibit certain cytochrome P450 enzymes (including CYP3A4, CYP2D6, CYP2C8, and CYP2C19). Inhibition of these enzymes may result in increased plasma levels of certain drugs, including cyclosporine and tacrolimus [see Drug Interactions (7.5, 7.6)]. The altered pharmacokinetics may necessitate dosage adjustment of the affected drug or discontinuation of treatment.

4. Editorial revisions to include an update to the Contents, re-numbering of the Drug Interactions section, and the addition of Exela Pharmaceuticals as a manufacturer were noted.
5. The revision date and version number was updated.

APPROVAL & LABELING

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at

<http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include 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).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials

should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Lori Anne Wachter, RN, BSN, RAC
Regulatory Project Manager for Safety
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD.
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

MARY R SOUTHWORTH
09/23/2016