



NDA 022276

LABELING ORDER

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 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nicardipine Hydrochloride 2.5 mg/mL for Injection.

On July 18, 2016, we sent you a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related label changes to the labeling of Nicardipine Hydrochloride for Injection to address the risk of a drug-drug interaction when nicardipine is used concomitantly with tacrolimus, which could result in elevated tacrolimus levels. The decision to require safety labeling changes was based on new safety information about this risk identified since this product was approved. You were directed to submit, within 30 days of the date of that letter, a supplement proposing changes to the approved labeling, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

The 30 days have passed and we have not received any submission from you addressing our letter dated July 18, 2016.

You failed to respond to our July 18, 2016, letter within 30 days. Under the authority of Section 505(o)(4)(E), we are ordering you to make all of the changes in the labeling listed in the July 18, 2016, letter (attached).

Pursuant to Section 505(o)(4)(E), a changes being effected (CBE) supplement containing all of the changes to the labeling that are listed in the July 18, 2016, letter must be received by FDA by September 22, 2016.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

SAFETY LABELING CHANGES UNDER 505(o)(4) – CHANGES BEING EFFECTED

Alternatively, by September 12, 2016, you may appeal this Order using the Agency's established

formal dispute resolution process as described in 21 CFR 10.75 and the Guidance for Industry, “Formal Dispute Resolution: Appeals Above the Division Level.”

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM343101.pdf>. The appeal should be submitted as a correspondence to your NDA referenced above. Identify the submission as “**Formal Dispute Resolution Request**” both on the cover letter and on the outside envelope. A copy of the submission should be sent to:

Kushboo Sharma
CDER Formal Dispute Resolution Project Manager
Food and Drug Administration
Office of New Drugs
Building 22, Room 6468
10903 New Hampshire Avenue
Silver Spring, MD 20993

In addition, to expedite coordination of any such appeal, a copy of the submission should also be sent to:

Lori Anne Wachter RN, BSN, RAC
Safety Regulatory Project Manager
Food and Drug Administration
Division of Cardiovascular and Renal Products
Building 22, Room 4158
10903 New Hampshire Avenue
Silver Spring, MD 20993

Refer to the Guidance for Industry, “Formal Dispute Resolution: Appeals Above the Division Level” for further instruction regarding the content and format of your request. Questions regarding the formal dispute resolution process may be directed to Kushboo Sharma, CDER Formal Dispute Resolution Project Manager, at (301) 301-796-1270. Appeals received by the Agency later than September 12, 2016, will not be entertained.

Failure to respond to this Order within the specified timeframes is a violation of section 505(o)(4) of the FDCA and could subject you to civil monetary penalties under section 303(f)(4) of the FDCA, 21 U.S.C. 333(f)(4), in the amount of up to \$250,000 per violation, with additional penalties if the violation continues uncorrected. Further, such a violation would cause your product to be misbranded under section 502(z) of the Act, 21 U.S.C. 352(z), which could subject you to additional enforcement actions, included but not limited to seizure of your product and injunction.

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}

Ellis F. Unger, MD
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE: Safety Labeling Change Notification Letter



NDA 022276

SAFETY LABELING CHANGE NOTIFICATION

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 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nicardipine Hydrochloride Injection 2.5 mg/mL.

Section 505(o)(4) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to make safety related label changes based upon new safety information that becomes available after approval of the drug or biological product.

Since Nicardipine Hydrochloride for Injection was approved on July 24, 2008, we have become aware of a drug-drug interaction with tacrolimus and nicardipine which could result in elevated tacrolimus levels if the drugs are co-administered. We consider this information to be “new safety information” as defined in section 505-1(b)(3) of the FDCA.

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above and in literature (e.g., Hooper DK, Fukuda T, Gardiner R, et al. Risk of tacrolimus toxicity in CYP3A5 nonexpressors treated with intravenous nicardipine after kidney transplantation. Transplantation 2012; 8: 806-12.), we believe that the new safety information should be included in the labeling for nicardipine products as follows (additions are shown as underlined text and deletions are shown as ~~striketrough~~ text):

1. In **HIGHLIGHTS/DRUG INTERACTIONS**, add the following text to the second bullet:

Nicardipine may increases cyclosporine and tacrolimus plasma levels. Frequent monitoring of trough blood levels of cyclosporine and tacrolimus is recommended when co-administering Cardene I.V. Premixed Injection. (7.3, 7.4)~~Monitor cyclosporine levels when co-administering with nicardipine. (7.5)~~

2. Under **DRUG INTERACTIONS**, add the following text:

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. Monitor closely plasma concentrations of cyclosporine during nicardipine hydrochloride injection administration, and adjust 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 Cardene I.V. Premixed Injection administration, and adjust the dose of tacrolimus accordingly.

3. Under **PHARMACOKINETICS/Metabolism and Excretion**, add the following text to the first paragraph:

Nicardipine 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 (7.5, 7.6). The altered pharmacokinetics may necessitate dosage adjustment of the affected drug or discontinuation of treatment.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a rebuttal statement detailing the reasons why such a change is not warranted. If you submit a supplement that includes only language identical to that specified above, the supplement may be submitted as a changes being effected (CBE-0) supplement. If the supplement includes proposed language that differs from that above, submit a prior approval supplement (PAS).

Requirements under section 505(o)(4) apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug approved under an NDA, including discontinued products, unless approval of an application has been withdrawn in the Federal Register. Therefore, the requirements described in this letter apply to you, unless approval of your application has been withdrawn in the Federal Register.

Under section 502(z), failure to submit a response in 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – CHANGES BEING EFFECTED

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – REBUTTAL (CHANGE NOT WARRANTED).”

If you do not submit electronically, please send 5 copies of the submission.

If you have any questions, 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 New Drugs
Center for Drug Evaluation and Research

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/s/

MARY R SOUTHWORTH
07/18/2016

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

/s/

ELLIS F UNGER
09/07/2016