



NDA 50715/S-035
NDA 50716/S-038

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Ronald Van Valen
Executive Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07856-1080

Dear Mr. Van Valen:

Please refer to your Supplemental New Drug Applications (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

NDA Number	Supplement Number	Drug Product	Submission Date	Receipt Date
50-715	035	Neoral [®] Soft Gelatin Capsules (cyclosporine capsules, USP)	October 17, 2014	October 17, 2014
50-716	038	Neoral [®] Oral Solution (cyclosporine oral solution, USP)	October 17, 2014	October 17, 2014

We acknowledge receipt of your amendments dated March 4 and 11, 2015.

These “Prior Approval” supplemental new drug applications provides for revisions to the **PRECAUTIONS/Drug Interactions** section and the **ADVERSE REACTIONS/Postmarketing Experience, Kidney, Liver and Heart Transplantation** section of the package inserts.

We have completed our review of these applications, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text, which is identical to the labeling text submitted on March 11, 2015.

LABELING REVISIONS

The revisions to the package inserts are as follows: (added text is double underlined, and deleted text is ~~strikethrough~~.)

1. The **PRECAUTIONS/Drug Interactions/2. Drugs/Dietary Supplements That Decrease Cyclosporine Concentrations/Bosentan** subsection has been revised as follows:

Bosentan

Co-administration of bosentan (250 to 1000 mg every 12 hours based on tolerability) and cyclosporine (300 mg every 12 hours for 2 days then dosing to achieve a C_{min} of 200 to 250 ng/mL) for 7 days in healthy subjects resulted in decreases in the cyclosporine mean dose-normalized AUC, C_{max} , and trough concentration of approximately 50%, 30% and 60%, respectively, compared to when cyclosporine was given alone. (*See also Effect of Cyclosporine on the Pharmacokinetics and/or Safety of Other Drugs or Agents*) Coadministration of cyclosporine with bosentan should be avoided.

2. In the **PRECAUTIONS/Drug Interactions/B. Effect of Cyclosporine on the Pharmacokinetics and/or Safety of Other Drugs or Agents** subsection, the following paragraphs are revised as follows:

Cyclosporine is an inhibitor of CYP3A4 and of ~~the~~ multiple drug efflux transporters (e.g., P-glycoprotein) and may increase plasma concentrations of comedications that are substrates of CYP3A4, ~~or~~ P-glycoprotein or both organic anion transporter proteins.

Cyclosporine may reduce the clearance of digoxin, colchicine, prednisolone, HMG-CoA reductase inhibitors (statins) and aliskiren, bosentan, dabigatran, repaglinide, NSAIDs, sirolimus, etoposide, and other drugs.

See the full prescribing information of the other drug for further information and specific recommendations. The decision on coadministration of cyclosporine with other drugs or agents should be made by the ~~physician~~ healthcare provider following the careful assessment of benefits and risks.

Ambrisentan

Coadministration of ambrisentan (5 mg daily) and cyclosporine (100 to 150 mg twice daily initially, then dosing to achieve C_{min} 150 to 200 ng/mL) for 8 days in healthy subjects resulted mean increases in ambrisentan AUC and C_{max} of approximately 2-fold and 1.5-fold, respectively, compared to ambrisentan alone. When coadministering ambrisentan with cyclosporine, the ambrisentan dose should not be titrated to the recommended maximum daily dose.

Bosentan

In healthy subjects, coadministration of bosentan and cyclosporine resulted in time-dependent mean increases in dose-normalized bosentan trough concentrations (i.e., on day 1 and day 8 of approximately 21-fold on day 1 and 2-fold on day 8 (steady state)) respectively compared to when bosentan was given alone as a single dose on day 1. (*See also Effect of Drugs and Other Agents on Cyclosporine Pharmacokinetics and/or Safety*) Coadministration of cyclosporine with bosentan should be avoided.

Dabigatran

The effect of cyclosporine on dabigatran concentrations had not been formally studied. Concomitant administration of dabigatran and cyclosporine may result in increased plasma

dabigatran concentrations due to the P-gp inhibitory activity of cyclosporine. Coadministration of cyclosporine with dabigatran should be avoided.

3. In the **ADVERSE REACTIONS/Postmarketing Experience, Kidney, Liver and Heart Transplantation** subsection, a new paragraph titled “Pain of lower extremities” is added as follows:

Pain of lower extremities

Isolated cases of pain of lower extremities have been reported in association with cyclosporine. Pain of lower extremities has also been noted as part of Calcineurin-Inhibitor Induced Pain Syndrome (CIPS) as described in the literature.

4. Numerous editorial changes throughout the labeling.

LABELING

Submit final printed labeling, as soon as they are available, but no more than 30 days after they are printed. The final printed labeling (FPL) must be identical to enclosed labeling (package insert) and must be in the “Drug Facts” format (21 CFR 201.66), where applicable.

The final printed labeling should be submitted electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Labeling for approved NDA 50715/S-035 and NDA 50716/S-038.**” Approval of this submission by FDA is not required before the labeling is used.

DRUG REGISTRATION AND LISTING

All drug establishment registration and drug listing information is to be submitted to FDA electronically, via the FDA automated system for processing structured product labeling (SPL) files (eLIST). At the time that you submit your final printed labeling (FPL), the content of labeling (Drug Facts) should be submitted in SPL format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. 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/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>. In addition, representative container or carton labeling, whichever includes Drug Facts, (where differences exist only in the quantity of contents statement) should be submitted as a JPG file.

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, call Ms. June Germain, Safety Regulatory Project Manager, at (301) 301-796-4024.

Sincerely,

{See appended electronic signature page}

Ozlem Belen, MD, MPH
Deputy Director for Safety
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE: Package insert

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

/s/

OZLEM A BELEN
03/31/2015