DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 019734/S-027

SUPPLEMENT APPROVAL

Chiesi USA, Inc.
Attention: Jessica Anderson, RAC
Manager, Regulatory Affairs
1255 Crescent Green Drive
Suite 250
Cary, NC 27518

Dear Ms. Anderson:

Please refer to your Supplemental New Drug Application (sNDA) dated and received March 9, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Cardene IV (nicardipine hydrochloride) Premixed Injection.

This supplemental new drug application provides for the following labeling revisions (additions are shown as underlined text and deletions are shown as ~~strikethrough~~ text):

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

   Oral or intravenous nicardipine may increase~~s~~ 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 Cardene I.V. Premixed Injection. (7.3)~~

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

   7.3 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.

   7.4 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**, the following text was added/deleted:

> Cardene I.V. has been shown to be rapidly and extensively metabolized by the 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 (7.3, 7.4). The altered pharmacokinetics may necessitate dosage adjustment of the affected drug or discontinuation of treatment.

4. The revision date and version number was updated.

There were no other changes noted from the last approved label.

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).

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
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
08/26/2016