DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-526/S - 012

SUPPLEMENT APPROVAL

Gilead Sciences, Inc.
Attention: Ruth Lessard
Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Lessard:

Please refer to your Supplemental New Drug Application (sNDA) dated December 18, 2009, received December 21, 2009, submitted under section 505(b)/(1) of the Federal Food, Drug, and Cosmetic Act for Ranexa, (Ranolazine) 500 and 1000 mg Extended-Release Tablets.

We acknowledge receipt of your amendments dated May 11, June 3, June 17, and June 25, and September 7, 2010.

This "Prior Approval" supplemental new drug application provides for labeling changes based on results of a drug-drug interaction study evaluating the effect of ranolazine on the pharmacokinetics of metoprolol. Labeling has been revised as follows:

1. Under **DRUG INTERACTIONS/Effects of Ranolazine on Other Drugs**, the ***"Drugs Metabolized by CYP2D6"*** subsection has been changed from:

   > Ranolazine or its metabolites partially inhibit CYP2D6. There are no studies of concomitant use of Ranexa with other drugs metabolized by CYP2D6, such as tricyclic antidepressants and antipsychotics, but lower doses of CYP2D6 substrates may be required.

   To:

   > Ranexa 750 mg twice daily increased the plasma concentrations of a single dose of immediate-release metoprolol (100 mg), a CYP2D6 substrate, by 1.8-fold. The exposure to other CYP2D6 substrates, such as tricyclic antidepressants and antipsychotics, may be increased during co-administration with Ranexa, and lower doses of these drugs may be required**.**

2. The following text has been moved from section 7.1 to section 12.3:

   > ***CYP2D6 Inhibitors***
   > The potent CYP2D6 inhibitor, paroxetine (20 mg once daily), increases ranolazine concentrations 1.2-fold. No dose adjustment of Ranexa is required in patients treated with CYP2D6 inhibitors.
   >
   > ***Digoxin***
   > Digoxin (0.125 mg) does not significantly alter ranolazine levels.

3. The following text has been moved from section 7.2 to section 12.3:

   Ranolazine and its most abundant metabolites are not known to inhibit the metabolism of substrates for CYP 1A2, 2C8, 2C9, 2C19, or 2E1 in human liver microsomes, suggesting that ranolazine is unlikely to alter the pharmacokinetics of drugs metabolized by these enzymes.

   Drugs Metabolized by CYP3A

   The plasma levels of simvastatin, a CYP3A substrate, and its active metabolite are each increased about 2-fold in healthy subjects receiving simvastatin (80 mg once daily) and Ranexa (1000 mg twice daily). Dose adjustments of simvastatin are not required when Ranexa is co-administered with simvastatin.

   The pharmacokinetics of diltiazem is not affected by ranolazine in healthy volunteers receiving diltiazem 60 mg three times daily and Ranexa 1000 mg twice daily.

4. Minor editorial changes and revisions have been made throughout the 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.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. 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 for this NDA, including pending "Changes Being Effected" (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.

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:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

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.(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

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:

Alexis Childers,
Regulatory Project Manager
(301) 796-0442.

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: Agreed-upon 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
09/23/2010