DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21526/S-026

SUPPLEMENT APPROVAL

Gilead Sciences, Inc.
Attention: Emmanuelle Bellemin
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Bellemin:

Please refer to your Supplemental New Drug Application (sNDA) dated May 2, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ranexa, (ranolazine) 500 and 1000 mg extended-release Tablets.

We acknowledge receipt of your amendments dated August 5, 14, November 15, December 4 and 11, 2013.

This Prior Approval supplemental new drug application provides for updates regarding severe renal impairment based on a clinical pharmacology study GS-US-259-0112. Minor editorial changes were made throughout the label. Content changes were made as follows:

1. Under **HIGHLIGHTS OF PRESCRIBING INFORMATION, WARNINGS AND PRECAUTIONS,** the following statement was added:

    - Renal failure: Monitor renal function after initiation and periodically in patients with moderate to severe renal impairment (CrCL < 60 mL/min). If acute renal failure develops, discontinue RANEXA. (5.2)

2. Under **FULL PRESCRIBING INFORMATION: CONTENTS**, section 5.2 was added to read:

    5.2 RENAL FAILURE

3. Under **WARNINGS AND PRECAUTIONS**, section 5.2 **Renal Impairment** was added to read as follows:

    Acute renal failure has been observed in some patients with severe renal impairment (creatinine clearance [CrCL] < 30 mL/min) while taking RANEXA. If acute renal failure develops (e.g., marked increase in serum creatinine associated with an increase in blood

urea nitrogen [BUN]), discontinue RANEXA and treat appropriately *[see Use in Specific Populations (8.7)]*.

4. Under **ADVERSE REACTIONS, Laboratory Abnormalities** the second paragraph was changed from:

   Ranexa produces elevations of serum creatinine by 0.1 mg/dL, regardless of previous renal function. The elevation has a rapid onset, shows no signs of progression during long-term therapy, is reversible after discontinuation of RANEXA, and is not accompanied by changes in BUN. In healthy volunteers,RANEXA 1000 mg twice daily had no effect upon the glomerular filtration rate. The elevated creatinine levels are likely due to a blockage of creatinine's tubular secretion by ranolazine or one of its metabolites.

To read as follows:

RANEXA produces elevations of serum creatinine by 0.1 mg/dL, regardless of previous renal function, likely because of inhibition of creatinine's tubular secretion. In general, the elevation has a rapid onset, shows no signs of progression during long-term therapy, is reversible after discontinuation of RANEXA, and is not accompanied by changes in BUN. In healthy volunteers, RANEXA 1000 mg twice daily had no effect upon the glomerular filtration rate. More marked and progressive increases in serum creatinine, associated with increases in BUN or potassium, indicating acute renal failure, have been reported after initiation of RANEXA in patients with severe renal impairment *[see Warnings and Precautions (5.2), Use in Specific Populations (8.7)]*.

5. Under **USE IN SPECIFIC POPULATIONS**, section 8.7 **Use in Patients with Renal Impairment** was changed from:

   Compared to patients with no renal impairment, C_{max} was increased between 40% and 50% in patients with mild, moderate or severe renal impairment, suggesting a similar increase in exposure in patients with renal failure independent of the degree of impairment. The pharmacokinetics of ranolazine has not been assessed in patients on dialysis.

   To read as follows:

   A pharmacokinetic study of RANEXA in subjects with severe renal impairment (CrCL < 30 mL/min) was stopped when 2 of 4 subjects developed acute renal failure after receiving RANEXA 500 mg twice daily for 5 days (lead-in phase) followed by 1000 mg twice a day (1 dose in one subject and 11 doses in the other). Increases in creatinine, BUN, and potassium were observed in 3 subjects during the 500 mg lead-in phase. One subject required hemodialysis, while the other 2 subjects improved upon drug discontinuation *[see Warnings and Precautions (5.2)]*. Monitor renal function

periodically in patients with moderate to severe renal impairment. Discontinue RANEXA if acute renal failure develops.

In a separate study, C_{max} was increased between 40% and 50% in patients with mild, moderate or severe renal impairment compared to patients with no renal impairment, suggesting a similar increase in exposure in patients with renal failure independent of the degree of impairment. The pharmacokinetics of ranolazine has not been assessed in patients on dialysis.

6. Under **PATIENT COUNSELING INFORMATION,** the following two bullet points were added:

    - to inform their physician if they have impaired renal function before or while taking RANEXA
    - that patients with severe renal impairment may be at risk of renal failure while on RANEXA

7. Under PATIENT INFORMATION**, What are possible side effects of RANEXA**, the following bullet was added:

    - kidney failure in people who already have severe kidney problems. Your doctor may need to do tests to check how your kidneys are working.

APPROVAL & 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 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, text for the patient 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 includes 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:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
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 314.81(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 Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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, at (301) 796-0442.

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, Pharm.D.
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
12/19/2013