DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21526/S-025

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 January 10. 2013, received, 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 February 28, July 29, August 16, September 20, and November 1, 2013.

This Prior Approval supplemental new drug application provides for updated postmarketing adverse events, instructions for co-administration with metformin, and a description of the drug interaction with atorvastatin. Minor editorial changes were made throughout the label. Content changes were made as follows:

1. Under **HIGHLIGHTS OF PRESCRIBING INFORMATION, DRUG INTERACTIONS,** a new bullet 4 was added and the previous bullet 4 (now bullet 5) was modified to read:
    - OCT2 substrates: Limit the dose of metformin to 1700 mg daily when used with RANEXA 1000 mg twice daily. Doses of other OCT2 substrates may require adjusted doses. (7.2)
    - Drugs transported by P-gp (e.g., digoxin), or drugs metabolized by CYP2D6 (e.g., tricyclic antidepressants): /May need reduced doses when used with RANEXA. (7.2)

2. Under **ADVERSE REACTIONS**, section 6.2 **Postmarketing Experience** was changed from:
   The following adverse reactions have been identified during postapproval use of Ranexa. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:
   Nervous System Disorders – tremor, paresthesia, hypoesthesia
   Psychiatric Disorders – hallucination

Skin and Subcutaneous Tissue Disorders – angioedema, rash, pruritus

To read as follows:

The following adverse reactions have been identified during postapproval use of RANEXA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Nervous System Disorders
Tremor, paresthesia, abnormal coordination, and other serious neurologic adverse events have been reported to occur, sometimes concurrently, in patients taking ranolazine. The onset of events was often associated with an increase in ranolazine dose or exposure. Many patients reported symptom resolution following drug discontinuation or dose decrease.
Psychiatric Disorders – hallucination
Renal and Urinary Disorders – dysuria, urinary retention
Skin and Subcutaneous Tissue Disorders – angioedema, pruritus, rash

3. Under **DRUG INTERACTIONS,** section 7.2 **Effects of Ranolazine on Other Drugs,** a new subsection was added to read as follows:

Drugs Transported by OCT2

In subjects with type 2 diabetes mellitus, concomitant use of RANXEA 1000 mg twice daily and metformin results in increased plasma levels of metformin. When RANEXA 1000 mg twice daily is co-administered with metformin, metformin dose should not exceed 1700 mg/day. Monitor blood glucose levels and risks associated with high exposures of metformin.
Metformin exposure was not significantly increased when given with RANEXA 500 mg twice daily *[see Clinical Pharmacology (12.3)]*.

4. Under **OVERDOSAGE,** the first paragraph was changed from:
High oral doses of ranolazine produce dose-related increases in dizziness, nausea, and vomiting. High intravenous exposure also produces diplopia, paresthesia, confusion, and syncope. In addition to general supportive measures, continuous ECG monitoring may be warranted in the event of overdose.

To read as follows:

High oral doses of ranolazine produce dose-related increases in dizziness, nausea, and vomiting. High intravenous exposure also produces diplopia, paresthesia, confusion, and syncope. In addition to general supportive measures, continuous ECG monitoring may be warranted in the event of overdose. Severe tremor, unsteady gait/incoordination, dysphasia, and hallucinations have been reported in cases of overdose with RANEXA.

5. Under **CLINICAL PHARMACOLOGY**, section 12.3 **Pharmacokinetics** subsection ***Drug Interactions, Strong CYP3A Inhibitors*** was changed from:
   Plasma levels of ranolazine with Ranexa 1000 mg twice daily are 3.2-fold higher if coadministered with ketoconazole 200 mg twice daily [*see Contraindications (4)*].

   To read as follows:
   Plasma levels of ranolazine with RANEXA 1000 mg twice daily are increased by 220% when coadministered with ketoconazole 200 mg twice daily *[see Contraindications (4)]*.

6. Under **CLINICAL PHARMACOLOGY,** section 12.3 **Pharmacokinetics** subsection ***Drug Interactions, CYP3A Substrates*** was changed from:
   The plasma levels of simvastatin, a CYP3A substrate, and its active metabolite are each doubled in healthy subjects receiving 80 mg once daily and Ranexa 1000 mg twice daily [*see Drug Interactions (7.2)]*.

To read as follows:

The plasma levels of simvastatin, a CYP3A substrate, and its active metabolite are increased by 100% in healthy volunteers receiving 80 mg once daily and RANEXA 1000 mg twice daily *[see Drug Interactions (7.2)]*. Mean exposure to atorvastatin (80 mg daily) is increased by 40% following co-administration with RANEXA (1000 mg twice daily) in healthy volunteers. However, in one subject the exposure to atorvastatin and metabolites was increased by ~400% in the presence of RANEXA.

7. Under **CLINICAL PHARMACOLOGY,** section 12.3 **Pharmacokinetics** subsection **Drug Interactions,** a new subsection was added as follows:
   OCT2 Substrates
   In subjects with type 2 diabetes mellitus, the exposure to metformin is increased by 40% and 80% following administration of ranolazine 500 mg twice daily and 1000 mg twice daily, respectively. If co-administered with RANEXA 1000 mg twice daily, do not exceed metformin doses of 1700 mg/day *[see Drug Interactions (7.2)]*.

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
11/12/2013