DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21526/S-014

SUPPLEMENT APPROVAL

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

Dear Mrs. Bellemin:

Please refer to your Supplemental New Drug Application (sNDA) dated October 1, 2010, received October 4, 2010 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 March 28, May 5, June 17, and July 8, 2011.

This "Prior Approval" supplemental new drug application provides for labeling changes to include a new section for adverse reactions, updated dosing information for patients with renal and/or hepatic impairment and updated information regarding co-administration with CYP3A and P-gp inhibitors. The label also includes information on dosing of simvastatin when co-administered with Ranexa. Labeling has been revised as follows:

1. Under **HIGHLIGHTS OF PRESCRIBING INFORMATION** the **CONTRAINDICATIONS** section was changed from:
    - Use with strong CYP3A inhibitors (e.g., ketoconazole, clarithromycin, nelfinavir) (4, 7.1)
    - Use with CYP3A inducers (e.g., rifampin, phenobarbital) (4, 7.1)
    - Use in patients with clinically significant hepatic impairment (4, 8.6)

    To read as follows:
    - Strong CYP3A inhibitors (e.g., ketoconazole, clarithromycin, nelfinavir) (4, 7.1)
    - CYP3A inducers (e.g., rifampin, phenobarbital, St. John's wort) (4, 7.1)
    - Liver cirrhosis (4, 8.6)

2. Under **HIGHLIGHTS OF PRESCRIBING INFORMATION** the **WARNINGS AND PRECAUTIONS** section was changed from:

    QT interval prolongation: Can occur with ranolazine. Little data available on high doses, long exposure, use with QT interval-prolonging drugs, or potassium channel variants causing prolonged QT interval. (5.1)

    To read as follows:

    QT interval prolongation: Can occur with ranolazine. Little data available on high doses, long exposure, use with QT interval-prolonging drugs, potassium channel variants causing prolonged QT interval, in patients with a family history of (or congenital) long QT syndrome, or in patients with known acquired QT interval prolongation. (5.1)

3. Under **HIGHLIGHTS OF PRESCRIBING INFORMATION** the first three bullets of the **DRUG INTERACTIONS** section was changed from:
    - CYP3A inhibitors: Do not use Ranexa with strong CYP3A inhibitors. With moderate 3A inhibitors (e.g., diltiazem, verapamil, erythromycin), limit maximum dose of Ranexa to 500 mg twice daily. (7.1)
    - CYP3A inducers: Do not use Ranexa with CYP3A inducers. (7.1)
    - P-gp inhibitors (e.g., cyclosporine): May need to lower Ranexa dose based on clinical response. (7.1)

    To read as follows:
    - Moderate CYP3A inhibitors (e.g., diltiazem, verapamil, erythromycin): Limit Ranexa to 500 mg twice daily. (7.1)
    - P-gp inhibitors (e.g., cyclosporine): Ranolazine exposure increased. Titrate Ranexa based on clinical response. (7.1)
    - CYP3A substrates: Limit simvastatin to 20 mg when used with Ranexa. Doses of other sensitive CYP3A substrates (e.g., lovastatin) and CYP3A substrates with narrow therapeutic range (e.g., cyclosporine, tacrolimus, sirolimus) may need to be reduced with Ranexa. (7.2)

4. Under **FULL PRESCRIBING INFORMATION: CONTENTS, ADVERSE REACTIONS**, section 6.2, Postmarketing Experience was added.

5. Under **DOSAGE AND ADMINISTRATION,** section 2.2 **Dose Modification,** was changed from:

    Dose adjustments may be needed when Ranexa is taken in combination with certain other drugs *[see Drug Interactions (7.1)]*. Limit the maximum dose of Ranexa to 500 mg twice daily in patients on diltiazem, verapamil, and other moderate CYP3A inhibitors. Down-titrate Ranexa based on clinical response in patients concomitantly treated with P-gp inhibitors, such as cyclosporine.

    To read as follows:

    Dose adjustments may be needed when Ranexa is taken in combination with certain other drugs *[see Drug Interactions (7.1)]*. Limit the maximum dose of Ranexa to 500 mg twice daily in patients on moderate CYP3A inhibitors such as diltiazem, verapamil, and erythromycin. Use of Ranexa with strong CYP3A inhibitors is contraindicated *[see Contraindications (4), Drug Interactions (7.1)]*.

    Use of P-gp inhibitors, such as cyclosporine, may increase exposure to Ranexa. Titrate Ranexa based on clinical response *[see Drug Interactions (7.1)]*.

6. Under **CONTRAINDICATIONS,** the third bullet was changed from:
    - With clinically significant hepatic impairment *[see Use in Specific Populations (8.6)]*

    To read as follows:
    - With liver cirrhosis *[see Use in Specific Populations (8.6)]*

7. Under **WARNINGS AND PRECAUTIONS,** section 5.1 **QT Interval Prolongation,** the second sentence in paragraph two was changed from:

However, there is little experience with high doses (> 1000 mg twice daily) or exposure, other QT-prolonging drugs, or potassium channel variants resulting in a long QT interval.

To read as follows:

However, there is little experience with high doses (> 1000 mg twice daily) or exposure, other QT-prolonging drugs, potassium channel variants resulting in a long QT interval, in patients with a family history of (or congenital) long QT syndrome, or in patients with known acquired QT interval prolongation.

8. Under **ADVERSE REACTIONS**, section 6.1 **Clinical Trial Experience,** paragraph 5 and 6 were changed from:

The following additional adverse reactions occurred at an incidence of 0.5 to 2.0% in patients treated with Ranexa and were more frequent than the incidence observed in placebo-treated patients:

Cardiac Disorders – bradycardia, palpitations
Ear and Labyrinth Disorders – tinnitus, vertigo
Gastrointestinal Disorders – abdominal pain, dry mouth, vomiting
General Disorders and Administrative Site Adverse Events – peripheral edema
Respiratory, Thoracic, and Mediastinal Disorders – dyspnea
Vascular Disorders – hypotension, orthostatic hypotension

Other (< 0.5%) but potentially medically important adverse reactions observed more frequently with Ranexa than placebo treatment in all controlled studies included: angioedema, renal failure, eosinophilia, blurred vision, confusional state, hematuria, hypoesthesia, paresthesia, tremor, pulmonary fibrosis, thrombocytopenia, leukopenia, and pancytopenia.

To read as follows:

The following additional adverse reactions occurred at an incidence of 0.5 to 4.0% in patients treated with Ranexa and were more frequent than the incidence observed in placebo-treated patients:

Cardiac Disorders – bradycardia, palpitations
Ear and Labyrinth Disorders – tinnitus, vertigo
Eye Disorders – blurred vision
Gastrointestinal Disorders – abdominal pain, dry mouth, vomiting, dyspepsia
General Disorders and Administrative Site Adverse Events – asthenia, peripheral edema
Metabolism and Nutrition Disorders – anorexia
Nervous System Disorders – syncope (vasovagal)
Psychiatric Disorders – confusional state
Renal and Urinary Disorders – hematuria
Respiratory, Thoracic, and Mediastinal Disorders – dyspnea
Skin and Subcutaneous Tissue Disorders – hyperhidrosis
Vascular Disorders – hypotension, orthostatic hypotension

Other (< 0.5%) but potentially medically important adverse reactions observed more frequently with Ranexa than placebo treatment in all controlled studies included: angioedema, renal failure, eosinophilia, chromaturia, blood urea increased, hypoesthesia, paresthesia, tremor, pulmonary fibrosis, thrombocytopenia, leukopenia, and pancytopenia.

9. Under **ADVERSE REACTIONS,** section 6.2 **Postmarketing Experience** was added 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, hypoesthesia
   Psychiatric disorders – hallucination
   Skin and Subcutaneous Tissue Disorders – angioedema, rash, pruritus

10. Some language under **DRUG INTERACTIONS,** section 7.1 **Effects of Other Drugs on Ranolazine** and 7.2 **Effects of Ranolazine on Other Drugs** was moved to section 12, and new subheaders in each section were added. Under section 7.2 a new subheader entitled **Drugs Metabolized by CYP3A** was added to include information on dosing with simvastatin. Section 7 now reads as follows:

7.1 Effects of Other Drugs on Ranolazine

Strong CYP3A Inhibitors

Do not use Ranexa with strong CYP3A inhibitors, including ketoconazole, itraconazole, clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir, and saquinavir *[see Contraindications (4), Clinical Pharmacology (12.3)]*.

Moderate CYP3A Inhibitors

Limit the dose of Ranexa to 500 mg twice daily in patients on moderate CYP3A inhibitors, including diltiazem, verapamil, erythromycin, fluconazole, and grapefruit juice or grapefruit-containing products *[see Dosage and Administration (2.2), Clinical Pharmacology (12.3)]*.

P-gp Inhibitors

Concomitant use of Ranexa and P-gp inhibitors, such as cyclosporine, may result in increases in ranolazine concentrations. Titrate Ranexa based on clinical response in patients concomitantly treated with predominant P-gp inhibitors such as cyclosporine *[see Dosage and Administration (2.2)]*.

CYP3A Inducers

Do not use Ranexa with CYP3A inducers such as rifampin, rifabutin, rifapentin, phenobarbital, phenytoin, carbamazepine, and St. John's wort *[see Contraindications (4), Clinical Pharmacology (12.3)]*.

7.2 Effects of Ranolazine on Other Drugs

Drugs Metabolized by CYP3A

Limit the dose of simvastatin in patients on any dose of Ranexa to 20 mg once daily, when ranolazine is co-administered. Dose adjustment of other sensitive CYP3A substrates (e.g., lovastatin) and CYP3A substrates with a narrow therapeutic range (e.g., cyclosporine, tacrolimus, sirolimus) may be required as Ranexa may increase plasma concentrations of these drugs *[see Clinical Pharmacology (12.3)]*.

Drugs Transported by P-gp

Concomitant use of ranolazine and digoxin results in increased exposure to digoxin. The dose of digoxin may have to be adjusted *[see Clinical Pharmacology (12.3)]*.

Drugs Metabolized by CYP2D6

The exposure to 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**.**

11. Under **USE IN SPECIFIC POPULATIONS,** section 8.6 **Use in Patients with Hepatic Impairment,** the paragraph was changed from:

    Ranexa is contraindicated in patients with clinically significant hepatic impairment. Plasma concentrations of ranolazine were increased by 30% in patients with mild (Child-Pugh Class A) and by 60% in patients with moderate (Child-Pugh Class B) hepatic impairment. This was not enough to account for the 3-fold increase in QT prolongation seen in patients with mild to severe hepatic impairment *[see Contraindications (4)]*.

    To read as follows:

    Ranexa is contraindicated in patients with liver cirrhosis. In a study of cirrhotic patients, the Cmax of ranolazine was increased 30% in cirrhotic patients with mild (Child-Pugh Class A) hepatic impairment, but increased 80% in cirrhotic patients with moderate (Child-Pugh Class B) hepatic impairment compared to patients without hepatic impairment. This increase was not enough to account for the 3-fold increase in QT prolongation seen in cirrhotic patients with mild to moderate hepatic impairment *[see Clinical Pharmacology (12.2)]*.

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

    In patients with varying degrees of renal impairment, ranolazine plasma levels increased up to 50%. The pharmacokinetics of ranolazine has not been assessed in patients on dialysis.

    To read as follows:

    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 *[see Dosage and Administration (2.2)]*. The pharmacokinetics of ranolazine has not been assessed in patients on dialysis.

13. Under **CLINICAL PHARMACOLOGY, SECTION 12.3 Pharmacokinetics** subsection ***Drug Interactions,*** the entire section was rewritten to include wording that was moved from section 7 and to include new subheaders. The section was changed from:

    Effect of other drugs on ranolazine

    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.

Effect of ranolazine on other drugs

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.

To read as follows:

Effect of other drugs on ranolazine

In vitro data indicate that ranolazine is a substrate of CYP3A and, to a lesser degree, of CYP2D6. Ranolazine is also a substrate of P-glycoprotein.

Strong CYP3A Inhibitors

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)]*.

Moderate CYP3A Inhibitors

Plasma levels of ranolazine with Ranexa 1000 mg twice daily are increased about 50 to 130% by diltiazem 180 to 360 mg, respectively. Plasma levels of ranolazine by Ranexa 750 mg twice daily are increased about 100% by verapamil 120 mg three times daily *[see Drug Interactions 7.1]*.

Weak CYP3A Inhibitors

The weak CYP3A inhibitors simvastatin (20 mg once daily) and cimetidine (400 mg three times daily) do not increase the exposure to ranolazine in healthy volunteers.

CYP3A Inducers

Rifampin 600 mg once daily decreases the plasma concentrations of ranolazine (1000 mg twice daily) by approximately 95% *[see Contraindications (4)]*.

CYP2D6 Inhibitors

Paroxetine 20 mg once daily increased ranolazine concentrations 20% in healthy volunteers receiving Ranexa 1000 mg twice daily. No dose adjustment of Ranexa is required in patients treated with CYP2D6 inhibitors.

Digoxin
Plasma concentrations of ranolazine are not significantly altered by concomitant digoxin at 0.125 mg once daily.

Effect of ranolazine on other drugs

In vitro ranolazine and its O-demethylated metabolite are weak inhibitors of CYP3A and moderate inhibitors of CYP2D6 and P-gp. *In vitro* ranolazine is an inhibitor of OCT2.

CYP3A Substrates

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)]*.

Diltiazem
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.

P-gp Substrates
Ranolazine increases digoxin concentrations 50% in healthy volunteers receiving Ranexa 1000 mg twice daily and digoxin 0.125 mg once daily *[see Drug Interactions (7.2)]*.

CYP2D6 Substrates
Ranexa 750 mg twice daily increases the plasma concentrations of a single dose of immediate release metoprolol (100 mg), a CYP2D6 substrate, by 80% in extensive CYP2D6 metabolizers with no need for dose adjustment of metoprolol. In extensive metabolizers of dextromethorphan, a substrate of CYP2D6, ranolazine inhibits partially the formation of the main metabolite dextrorphan.

14. Under **PATIENT COUNSELING INFORMATION,** bullet point 7 was changed from:
    - to inform their physician if they are receiving drugs that are moderate CYP3A inhibitors (e.g., diltiazem, verapamil, erythromycin) or P-gp inhibitors (e.g., cyclosporine)

    To read as follows:
    - to inform their physician if they are receiving drugs that are moderate CYP3A inhibitors (e.g., diltiazem, verapamil, erythromycin)
15. Under **PATIENT COUNSELING INFORMATION,** a new bullet was added as bullet 8 to read as follows:
    - to inform their physician if they are receiving P-gp inhibitors (e.g., cyclosporine)
16. Under **PATIENT COUNSELING INFORMATION,** old bullet point 9 (new bullet 10) was changed from:
    - that Ranexa should generally not be used in patients with clinically significant liver impairment

    To read as follows:
    - that Ranexa should not be used in patients with liver cirrhosis

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, 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 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
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 314.81(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 Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

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
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
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
07/11/2011