DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22081/S-018

SUPPLEMENT APPROVAL

Gilead Sciences, Inc.
Attention: Ellen L. Shen, Ph.D.
Associate Manager, Regulatory Affairs
333 Lakeside Dr.
Foster City, CA 94404

Dear Dr. Shen:

Please refer to your supplemental New Drug Application (sNDA) dated December 10, 2010, received December 13, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Letairis (ambrisentan) 5 and 10 mg Tablets.

We also acknowledge receipt of your amendments dated January 11, February 15, March 18, May 2 and 12, June 24, and July 13, 2011.

This "Prior Approval" supplemental new drug application provides for revisions to the text under the section entitled **CLINICAL PHARMACOLOGY/Pharmacokinetics/Drug Interactions** of the Prescribing Information (PI).

In the **FULL PRESCRIBING INFORMATION** section of the package insert:

Added/revised the following text under **CLINICAL PHARMACOLOGY/Pharmacokinetics/Drug Interactions** (note: to a large extent, text has been replaced by two Forest Plots, specifically Figures 2 and 3 in the PI)

FROM

Drug Interactions

***In vitro* studies**
Studies with human liver tissue indicate that ambrisentan is metabolized by CYP3A, CYP2C19, and uridine 5'-diphosphate glucuronosyltransferases (UGTs) 1A9S, 2B7S, and 1A3S. *In vitro* studies suggest that ambrisentan is a substrate of the Organic Anion Transport Protein (OATP), and a substrate but not an inhibitor of P-glycoprotein (P-gp). Drug interactions might be expected because of these factors; however, a clinically relevant interaction has been demonstrated only with cyclosporine *[see Drug Interactions (7)]*. Ambrisentan does not inhibit or induce phase I or II drug metabolizing enzymes at clinically relevant concentrations.

***In vivo* studies**

Effect of other drugs on ambrisentan

The drug interaction potential of ambrisentan has been evaluated using a strong CYP3A inhibitor (ketoconazole), a strong CYP3A and CYP2C19 inducer (rifampin), a CYP2C19 inhibitor (omeprazole), OATP inhibitors (rifampin, cyclosporine), a P-gp, Breast Cancer Resistance Protein (BCRP), OATP1B1, OATP1B3, and CYP3A inhibitor (cyclosporine), a P-gp and UGT inducer (rifampin), and several substrates of CYPs and P-gp.

Cyclosporine: A 14-day repeated dose study in healthy volunteers evaluated the effect of a cyclosporine twice daily regimen (targeting a trough concentration of 150 – 200 ng/mL) on ambrisentan (5 mg once daily) and vice-versa. An about 2-fold increase in the AUC and an about 1.5-fold increase in C_{max} of ambrisentan were observed *[see Drug Interactions (7)]*.

Rifampin: Acute co-administration (3 days) of rifampin (600 mg once daily) was associated with a transient 2-fold increase in the AUC of ambrisentan (10 mg once daily) in healthy volunteers; however, by Day 7, co-administration of rifampin had no clinically relevant effect on AUC or C_{max} of ambrisentan.

Co-administration of ambrisentan with the following drugs does not result in clinically relevant changes in ambrisentan exposure:

- Ketoconazole
- Omeprazole
- Sildenafil
- Tadalafil

Effect of ambrisentan on other drugs

Co-administration of ambrisentan does not change the exposure to the following drugs:

- Cyclosporine
- Warfarin
- Digoxin
- Sildenafil
- Tadalafil
- Ethinylestradiol/Norethindrone

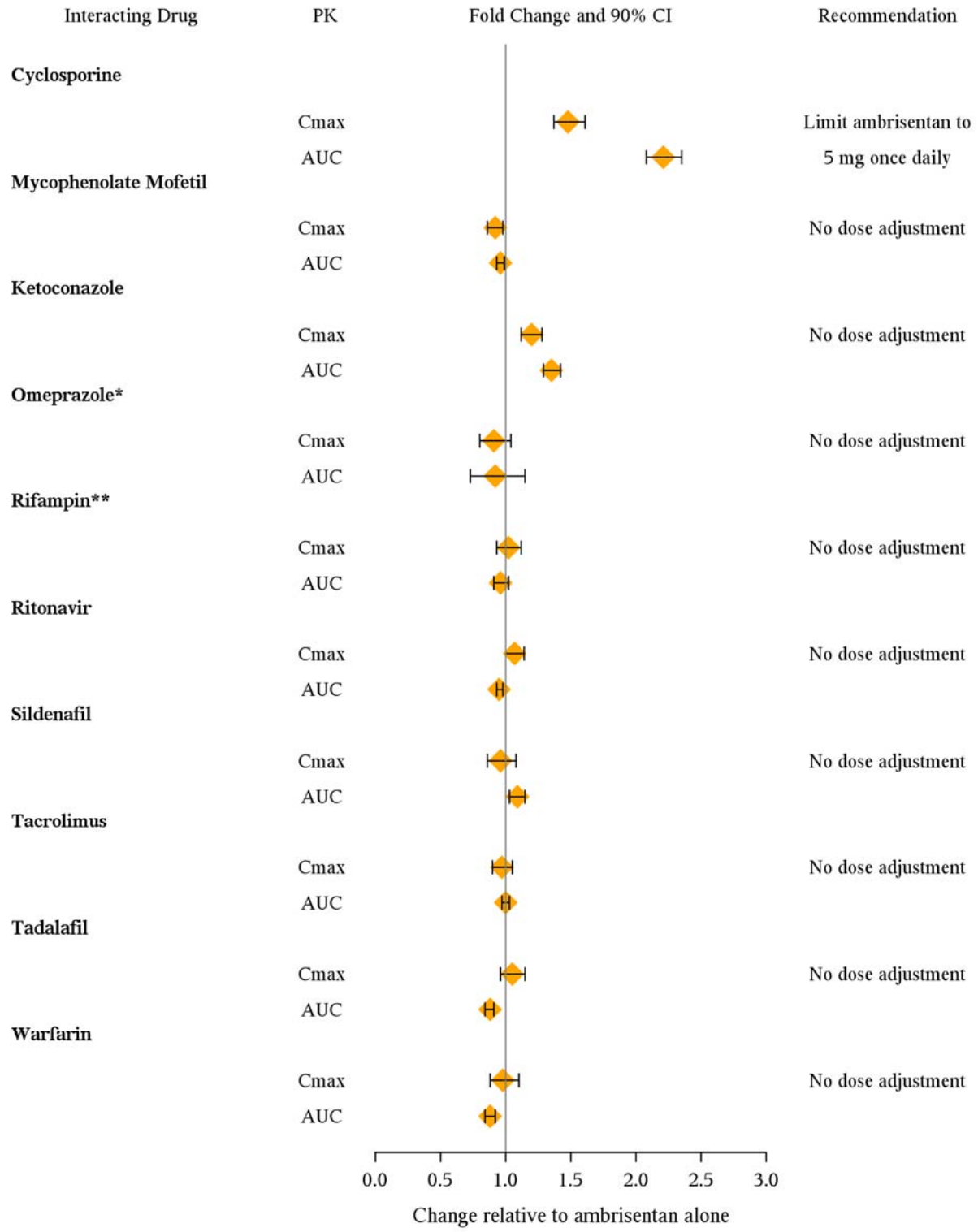
TO

Drug Interactions

***In vitro* studies**
Studies with human liver tissue indicate that ambrisentan is metabolized by CYP3A, CYP2C19, and uridine 5'-diphosphate glucuronosyltransferases (UGTs) 1A9S, 2B7S, and 1A3S. *In vitro* studies suggest that ambrisentan is a substrate of the Organic Anion Transporting Polypeptides OATP1B1 and OATP1B3, and a substrate but not an inhibitor of P-glycoprotein (P-gp). Drug interactions might be expected because of these factors; however, a clinically relevant interaction has been demonstrated only with cyclosporine *[see Drug Interactions (7)]*. Ambrisentan does not inhibit or induce drug metabolizing enzymes at clinically relevant concentrations.

***In vivo* studies**
The effects of other drugs on ambrisentan pharmacokinetics and the effects of ambrisentan on the exposure to other drugs are shown in Figure 2 and Figure 3, respectively.

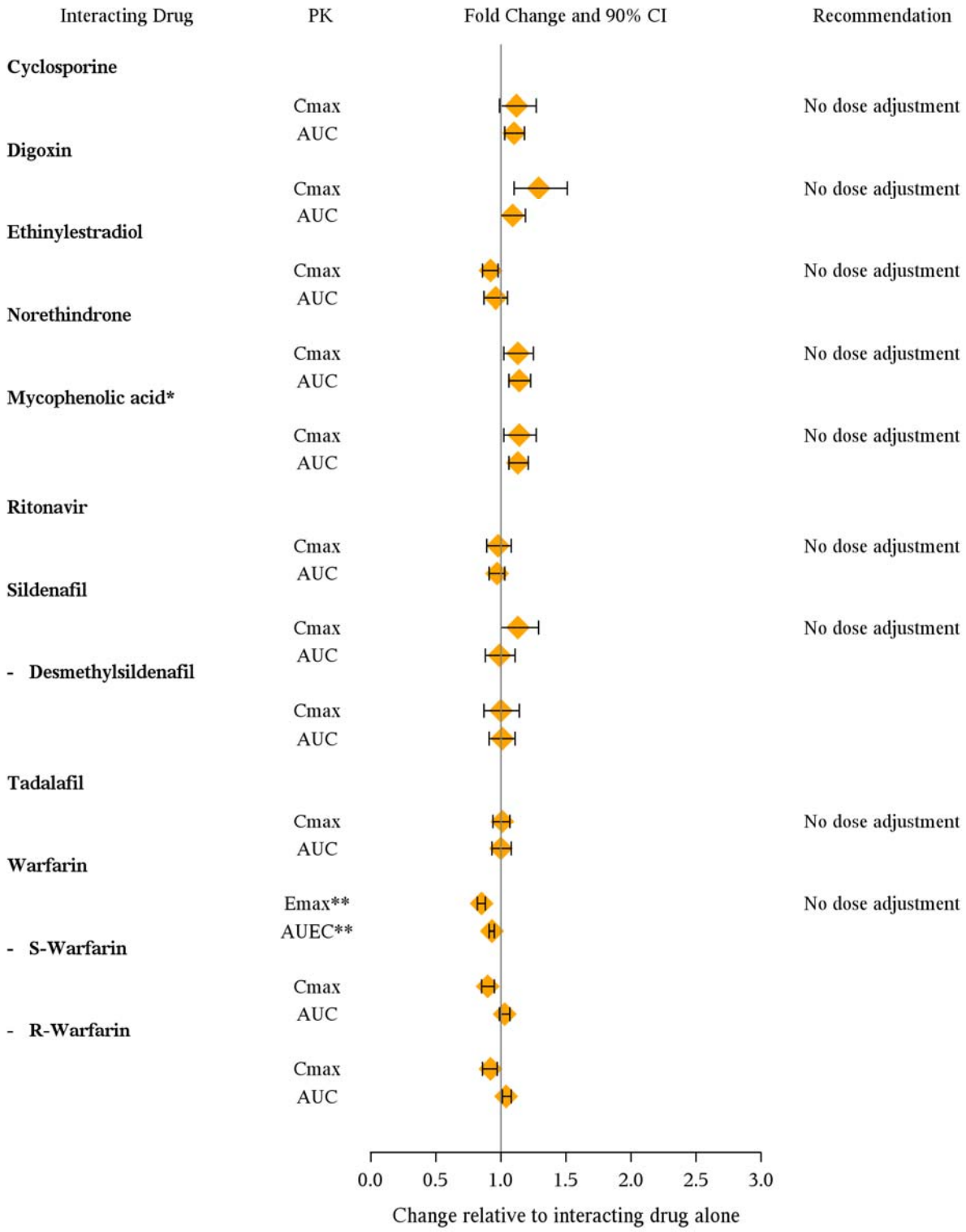
Figure 1 Effects of Other Drugs on Ambrisentan Pharmacokinetics



* Omeprazole: based on population pharmacokinetic analysis in PAH patients

** Rifampin: AUC and C_{max} were measured at steady-state. On Day 3 of co-administration a transient 2-fold increase in AUC was noted that was no longer evident by Day 7. Day 7 results are presented.

Figure 2 Effects of Ambrisentan on Other Drugs



* Active metabolite of mycophenolate mofetil

** GMR (95% CI) for INR

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, Medication Guide), 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).

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 Dan Brum, Pharm.D., BCPS, RAC, Regulatory Project Manager, at (301)796-0578.

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

Enclosures:

Package Insert

Medication Guide

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
07/19/2011