DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22081/S-029

SUPPLEMENT APPROVAL

Gilead Sciences, Inc.
Attention: Saima Malik, M.Sc.
Senior Associate, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Malik:

Please refer to your Supplemental New Drug Application (sNDA) dated September 23, 2013, received September 23, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Letairis (ambrisentan) 5 and 10 mg tablets.

We acknowledge receipt of your amendments dated February 13, April 4, and 17, 2014.

This "Prior Approval" supplemental new drug application proposes to add the results from the final study report for AD-300-2001, titled "Effect of Ambrisentan on Human Hepatic Uptake and Efflux Transporters". Additional minor editorial and formatting changes were also proposed.

In the **USE IN SPECIFIC POPULATIONS** section, subsection **8.8 Hepatic Impairment,** Pre-existing Hepatic Impairment of the package insert (additions noted in underline, deletions noted in strikethrough):

FROM:
The influence of pre-existing hepatic impairment on the pharmacokinetics of ambrisentan has not been evaluated. Because there is in vitro and in vivo evidence of significant metabolic and biliary contribution to the elimination of ambrisentan, hepatic impairment would be expected to have significant effects on the pharmacokinetics of ambrisentan [see Clinical Pharmacology (12.3)]. Letairis is not recommended in patients with moderate or severe hepatic impairment. There is no information on the use of Letairis in patients with mild pre-existing impaired liver function; however, exposure to ambrisentan may be increased in these patients.

TO:
The influence of pre-existing hepatic impairment on the pharmacokinetics of ambrisentan has not been evaluated. Because there is in vitro and in vivo evidence of significant metabolic and biliary contribution to the elimination of ambrisentan, hepatic impairment ~~would~~ might be expected to have significant effects on the pharmacokinetics of ambrisentan [see Clinical Pharmacology (12.3)]. Letairis is not recommended in patients with moderate or severe hepatic impairment.

There is no information on the use of Letairis in patients with mild pre-existing impaired liver function; however, exposure to ambrisentan may be increased in these patients.

In the **CLINICAL PHARMACOLOGY** section, subsection **12.3 Pharmacokinetics,** Drug Interactions, In Vitro Studies of the package insert:

FROM:
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.

TO:
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)]. In vitro studies found ambrisentan to have little to no inhibition of human hepatic transporters. Ambrisentan demonstrated weak dose-dependent inhibition of OATP1B1, OATP1B3, and NTCP (IC50 of 47 µM, 45 µM, and approximately 100 µM, respectively) and no transporter-specific inhibition of BSEP, BRCP, P-gp, or MRP2. Ambrisentan does not inhibit or induce drug metabolizing enzymes at clinically relevant concentrations.

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 and with the minor editorial revisions listed below.

1. In the **Highlights Limitation Statement,** LETAIRIS should appear in UPPER CASE letters in both uses of the drug product name.
2. The Boxed Warning in the Highlights and the Boxed Warning in the Full Prescribing Information should have the same cross-references.
3. Ensure the "Revised" month listed at the end of Highlights is the same as the supplement approval month.

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, except with the revisions indicated, the enclosed labeling (text for the 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 via 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 with the revisions indicated above 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/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. 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, call Wayne Amchin, Regulatory Project Manager, at (301) 796-0421.

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD
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
05/05/2014