



NDA 205834/S-2

**SUPPLEMENT APPROVAL**

Gilead Sciences, Inc.  
Attention: Prachi Shah, MBS, RAC  
Associate Manager, Regulatory Affairs  
333 Lakeside Drive  
Foster City, CA 94404

Dear Ms. Shah:

Please refer to your Supplemental New Drug Application (sNDA) dated and received May 14, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Harvoni<sup>®</sup> (ledipasvir/sofosbuvir), fixed-dose combination tablet, 90 mg/400 mg.

This Prior Approval supplemental new drug application proposes the following changes:

1. To expand the patient population to include patients with chronic hepatitis C virus infection who are co-infected with HIV-1 and to update various sections of the labeling based upon the results from GS-US-337-0115 (ION 4) study.
2. To update DRUG INTERACTIONS, Drugs without Clinically Significant Interactions subsection with information related to dolutegravir, and elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide combination therapy.
3. To update DRUG INTERACTIONS, Table 4 with information regarding drug interactions between Harvoni and regimens containing tenofovir DF without a HIV protease inhibitor/ritonavir or cobicistat, and drug interaction between Harvoni and antimycobacterials.
4. To update CLINICAL PHARMACOLOGY, Table 5 and Table 6 with drug interaction information between Harvoni and elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, atazanavir/ritonavir/emtricitabine/tenofovir DF, darunavir/ritonavir/emtricitabine/tenofovir DF, or rifampin.
5. To update the NONCLINICAL TOXICOLOGY, *Carcinogenesis, Mutagenesis, Impairment of Fertility* subsection with carcinogenicity data from the ledipasvir 6-month rasH2 transgenic mouse study and to remove the Animal Toxicology and/or Pharmacology section.

6. To update the “What should I tell my healthcare provider before taking Harvoni?” and “Especially tell your healthcare provider if you take any of the following medicines” sections of the Patient Information.

## **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 and 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).

## **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria applies to your application, you are exempt from this requirement.

## **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:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

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>.

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, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

## **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 Mammah Sia Borbor, Regulatory Project Manager, at (301) 796-7731.

Sincerely,

*{See appended electronic signature page}*

Debra Birnkrant, MD  
Director  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

ENCLOSURE:  
Content of Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DEBRA B BIRNKRANT  
11/12/2015