

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205834Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 205834

SUPPL #

HFD #

Trade Name HARVONI

Generic Name ledipasvir/sofosbuvir fixed-dosed combination tablet

Applicant Name Gilead Sciences

Approval Date, If Known

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

### **1. Single active ingredient product.**

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 204671

Sovaldi (sofosbuvir)

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

***NDA 205834 contains ledipasvir, a new chemical entity, in combination with sofosbuvir, a previously approved active moiety. Under the Agency's new interpretation described in the Agency's Guidance for Industry, New Chemical Entity Exclusivity for Certain Fixed-Combination Drug Products, a drug substance is eligible for 5-year exclusivity, provided it meets the regulatory definition of new chemical entity, regardless of whether that drug substance is approved in a single-ingredient drug product or in a fixed-combination with another drug substance that contains no previously approved active moiety, or in a fixed-combination with another drug substance that contains a previously approved active moiety. This NDA is thus eligible for 5-year new chemical entity exclusivity pursuant to the new interpretation.***

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

=====

Name of person completing form: Linda C. Onaga  
Title: Senior Regulatory Project Manager  
Date: October 10, 2014

Name of Office/Division Director signing form: Debra Birnkrant  
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12



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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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LINDA C ONAGA  
10/10/2014

DEBRA B BIRNKRANT  
10/10/2014

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 205834 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: HARVONI Established/Proper Name: ledipasvir/sofosbuvir tablet Dosage Form: tablet		Applicant: Gilead Sciences, Inc. Agent for Applicant (if applicable):
RPM: Linda C. Onaga, MPH		Division: Division of Antiviral Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <div style="margin-left: 20px;"> <input type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>)            Date of check:         </div> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>October 10, 2014</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☐ Standard ☒ Priority  
Chemical classification (new NDAs only):  
(confirm chemical classification at time of approval)

- |                                                                      |                                                   |
|----------------------------------------------------------------------|---------------------------------------------------|
| <input checked="" type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                              | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation                     | <input type="checkbox"/> Direct-to-OTC            |
| <input checked="" type="checkbox"/> Breakthrough Therapy designation |                                                   |

NDAs: Subpart H

- ☐ Accelerated approval (21 CFR 314.510)  
☐ Restricted distribution (21 CFR 314.520)

Subpart I

- ☐ Approval based on animal studies

- ☐ Submitted in response to a PMR  
☐ Submitted in response to a PMC  
☐ Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- ☐ Accelerated approval (21 CFR 601.41)  
☐ Restricted distribution (21 CFR 601.42)

Subpart H

- ☐ Approval based on animal studies

- REMS: ☐ MedGuide  
☐ Communication Plan  
☐ ETASU  
☐ MedGuide w/o REMS  
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other Listserv announcement
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	Action(s) and date(s) October 10, 2014
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
• Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
• Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) (indicate date(s))	May 2, 2014
• Review(s) (indicate date(s))	April 29, 2014
❖ Labeling reviews (indicate dates of reviews)	RPM: <input type="checkbox"/> None 3/27/14 DMEPA: <input type="checkbox"/> None 8/22/14 DMPP/PLT (DRISK): <input type="checkbox"/> None 8/26/14 OPDP: <input type="checkbox"/> None 8/26/14 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting (indicate date of each review)	March 31, 2014
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>This application is on the AIP <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>Date reviewed by PeRC <u>August 6, 2014</u> If PeRC review not necessary, explain: _____</li> </ul>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) ( <i>do not include previous action letters, as these are located elsewhere in package</i> )	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	None
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A   May 21, 2014
<ul style="list-style-type: none"> <li>Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A   August 7, 2014
<ul style="list-style-type: none"> <li>Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul>	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None   October 10, 2014
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None   September 23, 2014
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None   August 8, 2014
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None   9
<b>Clinical</b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	Review: July 10, 2014 Filing Checklist: March 11, 2014
<ul style="list-style-type: none"> <li>Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	Clinical Review, Page 199
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None   DTOP May 23, 2014 DHOP May 19, 2014
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A

❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	N/A  <input type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input type="checkbox"/> None requested June 23, 2014
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Review July 10, 2014 Filing Checklist March 11, 2014
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Review July 10, 2014 Filing Checklist March 12, 2014
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Review July 10, 2014 Filing Checklist March 11, 2014
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review July 15, 2014
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Review July 10, 2014 July 7, 2014 Filing Checklist March 11, 2014
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None May 28, 2014 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested



Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None July 11, 2014 July 10, 2014
❖ Microbiology Reviews	<input type="checkbox"/> Not needed March 31, 2014
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	N/A
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	Product Quality Review pg. 136
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	N/A
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	N/A
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup>)</i>	Date completed: Sept. 3, 2014 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>5</sup> i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>Finalize 505(b)(2) assessment</li> </ul>	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done



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LINDA C ONAGA  
10/10/2014

**From:** [Michele Anderson](#)  
**To:** [Onaga, Linda](#)  
**Cc:** [Regulatory Archives](#); [Prachi Shah](#)  
**Subject:** RE: IND 115268 and NDA 205834  
**Date:** Wednesday, September 17, 2014 4:36:10 PM

---

Hi Linda,

We agree to make this change and will submit a revised label ASAP.

Thank you,  
Michele

---

**From:** Onaga, Linda [<mailto:Linda.Onaga@fda.hhs.gov>]  
**Sent:** Wednesday, September 17, 2014 1:24 PM  
**To:** Michele Anderson  
**Cc:** Regulatory Archives; Prachi Shah  
**Subject:** RE: IND 115268 and NDA 205834

Michele,

We have an additional edit the Harvoni label:

Please modify the following sentence in Section 14 Microbiology

FROM: Sustained virologic response (SVR) was the primary endpoint (b) (4).  
(b) (4) was defined as HCV RNA less than LLOQ at 12 weeks after the cessation of treatment.

TO: Sustained virologic response (SVR) was the primary endpoint and was defined as HCV RNA less than LLOQ at 12 weeks after the cessation of treatment.

Please let me know if you agree to this change if so please submit a revised label

Linda.

---

**From:** Michele Anderson [<mailto:Michele.Anderson@gilead.com>]  
**Sent:** Wednesday, September 17, 2014 3:16 PM  
**To:** Onaga, Linda  
**Cc:** Regulatory Archives; Prachi Shah  
**Subject:** RE: IND 115268 and NDA 205834

Dear Linda,

Attached please find Gilead's response to the 16 September labeling comments for NDA 205834. We have agreed with all comments provided. This information will be submitted through the gateway shortly.

If you could let me know whether additional labeling comments should be expected I would appreciate it.

Thank you,  
Michele

---

**From:** Onaga, Linda [<mailto:Linda.Onaga@fda.hhs.gov>]  
**Sent:** Tuesday, September 16, 2014 1:58 PM  
**To:** Michele Anderson  
**Subject:** IND 115268 and NDA 205834

Good Afternoon Michele,

Please find attached comments for IND 115268 SD 190 and NDA 205834 labeling comments from the Division and SEALD team.

We request a response to the labeling comments by Thursday.

Thanks

Linda

*Linda C. Onaga, MPH  
Senior Regulatory Project Manager  
Division of Antiviral Products (DAVP)  
FDA/CDER/OND/OAP  
White Oak Complex, Bldg 22, Rm 6321  
10903 New Hampshire Ave.  
Silver Spring, MD 20993  
Ph: 301.796.0759  
Fax: 301.796.9883  
Email: [linda.onaga@fda.hhs.gov](mailto:linda.onaga@fda.hhs.gov)*

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/s/  
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LINDA C ONAGA  
09/24/2014

**From:** [Michele Anderson](#)  
**To:** [Onaga, Linda](#)  
**Cc:** [Jennifer Huber](#); [Prachi Shah](#)  
**Subject:** Re: NDA 205834 PMC  
**Date:** Wednesday, September 24, 2014 3:20:46 PM

---

Hi Linda  
Thank you for your email. We will respond today.  
Thanks,  
Michele

On Sep 24, 2014, at 8:06 PM, "Onaga, Linda"  
<[Linda.Onaga@fda.hhs.gov](mailto:Linda.Onaga@fda.hhs.gov)<<mailto:Linda.Onaga@fda.hhs.gov>>> wrote:

We request a response before close of business today.

Thanks

Linda

From: Onaga, Linda  
Sent: Wednesday, September 24, 2014 3:03 PM  
To: [michele.anderson@gilead.com](mailto:michele.anderson@gilead.com)<<mailto:michele.anderson@gilead.com>>; Jennifer Huber  
([Jennifer.Huber@gilead.com](mailto:Jennifer.Huber@gilead.com)<<mailto:Jennifer.Huber@gilead.com>>)  
Cc: Prachi Shah ([Prachi.Shah@gilead.com](mailto:Prachi.Shah@gilead.com)<<mailto:Prachi.Shah@gilead.com>>)  
Subject: NDA 205834 PMC  
Importance: High

Good Afternoon Michele,

Please find below an additional PMC that we are adding for the LDV/SOF NDA. Please provide timelines for the listed PMC.

PMC:

Submit an interim study report from the ongoing study GS-US-248-0122, entitled, "A Long Term Follow-up Registry for Subjects Who Achieve a Sustained Virologic Response to Treatment in Gilead-Sponsored Trials in Subjects with Chronic Hepatitis C Infection", with the three year follow-up data from: GS-US-337-0102 (ION-1), GS-US-337-0109 (ION-2), GS-US-337-0108 (ION-3).

PMR/PMC Schedule Milestones:

Final Protocol Submission:

Study/Trial Completion:

Final Report Submission:

Please submit your response by 9/25/14.

Thanks

Linda

Linda C. Onaga, MPH  
Senior Regulatory Project Manager  
Division of Antiviral Products (DAVP)  
FDA/CDER/OND/OAP  
White Oak Complex, Bldg 22, Rm 6321  
10903 New Hampshire Ave.  
Silver Spring, MD 20993  
Ph: 301.796.0759  
Fax: 301.796.9883  
Email: linda.onaga@fda.hhs.gov<<mailto:linda.onaga@fda.hhs.gov>>

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LINDA C ONAGA  
09/24/2014



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE**

**NDA:** 205834  
**Drug:** ledipasvir/sofosbuvir FDC  
**Date:** September 16, 2014  
**To:** Michele Anderson, Associate Director, Regulatory Affairs  
**Sponsor:** Gilead Sciences, Inc.  
**Subject:** NDA 205834 Rationale for Proposed Labeling Changes

---

Please find attached the Division's and SEALD team's labeling edits for NDA 205834. A word copy of the label will be attached to this correspondence.

Please provide your response by 4:00PM, Thursday, September 18, 2014

We are providing this above information via e-mail for your convenience. Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

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Linda C. Onaga, MPH  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/  
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LINDA C ONAGA  
09/16/2014



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE**

**NDA:** 205834  
**Drug:** ledipasvir/sofosbuvir FDC  
**Date:** September 2, 2014  
**To:** Michele Anderson, Associate Director, Regulatory Affairs  
**Sponsor:** Gilead Sciences, Inc.  
**Subject:** NDA 205834 Rationale for Proposed Labeling Changes

---

Please find attached the Division's labeling edits for NDA 205834. A word copy of the label will be attached to this correspondence.

We have no additional comments on the carton and container labeling.

We are providing this above information via e-mail for your convenience. Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

---

Linda C. Onaga, MPH  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/  
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LINDA C ONAGA  
09/02/2014

**PeRC PREA Subcommittee Meeting Minutes**  
**August 6, 2014**

**PeRC Members Attending:**

Lynne Yao  
Rosemary Addy  
Jane Inglese  
Hari Cheryl Sachs  
Tom Smith  
Peter Starke  
Andrew Mulberg  
Gregory Reaman  
Julia Pinto  
Kristiana Brugger  
Andrew Mosholder  
Lily Mulugeta  
Dianne Murphy

## Agenda

NDA	205834	Harvoni (ledipasvir/sofosbuvir) Partial Waiver/Deferral/Plan	Treatment of chronic hepatitis C infection in genotype 1 patients
(b) (4)			

### Harvoni (ledipasvir/sofosbuvir) Partial Waiver/Deferral/Plan

- NDA 205834 seeks marketing approval for Harvoni (ledipasvir/sofosbuvir) for treatment of chronic hepatitis C infection in genotype 1 patients
- The application triggers PREA as directed to a new active ingredient.
- The application has a PDUFA goal date of October 10, 2014.
- *PeRC Recommendations:*
  - The PeRC agreed with a partial waiver for pediatric patients aged birth to less than 3 years because studies would be impossible or highly impracticable.
  - The PeRC agreed with a deferral for pediatric patients aged 3 to less than 18 years because adult studies have been completed and the product is ready for approval. The Division clarified that a protocol for the pediatric efficacy study has already been submitted. The PeRC also agreed with the timeline for completion of the studies as proposed by the Division.

- (b) (4)

(b) (4)

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/s/  
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JANE E INGLESE  
08/18/2014



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE**

**NDA:** 205834  
**Drug:** ledipasvir/sofosbuvir FDC  
**Date:** August 14, 2014  
**To:** Michele Anderson, Associate Director, Regulatory Affairs  
**Sponsor:** Gilead Sciences, Inc.  
**Subject:** NDA 205834 PMR descriptions and timelines

---

Please find attached the Division's PMR descriptions for NDA 205834. Please provide timelines for each PMR listed.

**PMRs:**

1. Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of ledipasvir/sofosbuvir in pediatric subjects 3 through 17 years of age with chronic hepatitis C

Schedule Milestones:	Final Protocol Submission:	<u>07/2014</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other:	<u>MM/DD/YYYY</u>

2. Collect and analyze long-term safety data for subjects enrolled in the pediatric ledipasvir/sofosbuvir safety, pharmacokinetic and efficacy study. Data collected should include at least 3 years of follow-up in order to characterize the long-term safety of ledipasvir/sofosbuvir including growth assessment, sexual maturation and characterization of ledipasvir/sofosbuvir resistance associated substitutions in viral isolates from subjects failing therapy.

Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other:	<u>MM/DD/YYYY</u>

3. Submit the final report and datasets for the ongoing trial GS-US-337-0123, entitled "A Phase 2, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/Ledipasvir Fixed-Dose Combination + Ribavirin Administered in Subjects Infected with Chronic HCV who have Advanced Liver Disease or are Post-Liver Transplant", in order to provide safety data and dosing

recommendations for subjects with decompensated cirrhosis and/or in subjects receiving concomitant immunosuppressive agents post-liver transplant (e.g., cyclosporine).

Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other:	<u>MM/DD/YYYY</u>

4. Submit the final report and datasets for the ongoing trial GS-US-337-0115, entitled “A Phase 3, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination for 12 Weeks in Subjects with Chronic Genotype 1 or 4 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV)-1 Co-infection”, in order to obtain additional safety data in subjects receiving concomitant ledipasvir/sofosbuvir and Atripla (or its components) and to provide dosing recommendations for co-infected subjects.

Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other:	<u>MM/DD/YYYY</u>

5. Submit the ledipasvir two-year rat carcinogenicity study.

Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other:	<u>MM/DD/YYYY</u>

6. Submit the ledipasvir two-year mouse carcinogenicity study.

Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other:	<u>MM/DD/YYYY</u>

7. Submit longitudinal data on persistence of NS5A resistance substitutions from subjects who did not achieve SVR12 in Phase 2 studies of ledipasvir with other DAAs.

Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other:	<u>MM/DD/YYYY</u>

8. Conduct a study to assess the impact of NS5B substitutions A112T, E237G, and S473T on the phenotypic susceptibility of sofosbuvir in the GT1a HCV replicon system.

Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other:	<u>MM/DD/YYYY</u>



Please submit your response by August 22, 2014.

We are providing this above information via e-mail for your convenience. Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

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Linda C. Onaga, MPH  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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LINDA C ONAGA  
08/14/2014



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE**

**NDA:** 205834  
**Drug:** ledipasvir/sofosbuvir FDC  
**Date:** August 13, 2014  
**To:** Michele Anderson, Associate Director, Regulatory Affairs  
**Sponsor:** Gilead Sciences, Inc.  
**Subject:** NDA 205834 Rationale for Proposed Labeling Changes

---

Please find attached the Division's labeling edits for NDA 205834. A word copy of the label will be attached to this correspondence.

Please note that the Division did not incorporate revisions proposed by Gilead on August 11, 2014. Please review the Division comments and proposed your revisions accordingly.

Additionally, please update labeling with approved Trade Name.

We are providing this above information via e-mail for your convenience. Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

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Linda C. Onaga, MPH  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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LINDA C ONAGA  
08/13/2014

**From:** Onaga, Linda  
**To:** ["Michele Anderson"](#)  
**Subject:** RE: NDA 205834  
**Date:** Wednesday, August 06, 2014 10:43:00 AM

---

Good Morning Michele,

We appreciate Gilead's offer to provide 10 week data. However, we want to wait for the median 12 week data because a LDV/SOF 24-week regimen is recommended for some patients. Having the full median 12 week data will aid in informing labeling decisions.

Thanks

Linda

---

**From:** Michele Anderson [mailto:[Michele.Anderson@gilead.com](mailto:Michele.Anderson@gilead.com)]  
**Sent:** Tuesday, August 05, 2014 6:52 PM  
**To:** Onaga, Linda  
**Subject:** RE: NDA 205834

Dear Linda,

We acknowledge the RFI (below) and the request for additional safety data with median 12 week duration of study drug exposure from Study GS-US-337-0115. To inform labeling decisions and come to agreement at the LCM, would it be helpful for Gilead to provide the requested safety data with median 10.4 weeks of exposure with 45% of patients (n=72) through Week 12 at or prior to the LCM?

Please let me know as soon as possible.

Thank you,  
Michele

**Request for Information:**

Due to increased tenofovir exposures observed with LDV/SOF + Atripla co-administration, safety assessment in HCV infected subjects receiving this combination is important to inform labeling decisions. Therefore, we request the following information:

- GS-US-337-0115 additional safety data with median 12 week duration of study drug exposure, in a similar format to that provided in SN 24 (SDN 26)
- NIAID-13-I-0159:
  - Assessment of (1) hypophosphatemia and (2) increased creatinine, including breakdown by antiretroviral treatment regimen and if these laboratory changes occurred in the same subjects.
  - Similar to the prior -0115 safety assessment, identification of any subjects with:
    - treatment emergent normoglycemic glycosuria

- eGFR <50 mL/min
- ≥25% reduction in eGFR from baseline

---

**From:** Onaga, Linda [<mailto:Linda.Onaga@fda.hhs.gov>]

**Sent:** Tuesday, August 05, 2014 2:54 PM

**To:** Michele Anderson

**Subject:** NDA 205834

Good Afternoon Michele,

Please find attached comments and an updated agenda for Thursday's tcon for NDA 205834. We plan to send Gilead an updated label by COB tomorrow.

Thanks

Linda

*Linda C. Onaga, MPH  
Senior Regulatory Project Manager  
Division of Antiviral Products (DAVP)  
FDA/CDER/OND/OAP  
White Oak Complex, Bldg 22, Rm 6321  
10903 New Hampshire Ave.  
Silver Spring, MD 20993  
Ph: 301.796.0759  
Fax: 301.796.9883  
Email: [linda.onaga@fda.hhs.gov](mailto:linda.onaga@fda.hhs.gov)*

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LINDA C ONAGA  
08/06/2014



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE**

**NDA:** 205834  
**Drug:** ledipasvir/sofosbuvir FDC  
**Date:** July 28, 2014  
**To:** Michele Anderson, Associate Director, Regulatory Affairs  
**Sponsor:** Gilead Sciences, Inc.  
**Subject:** NDA 205834 Rationale for Proposed Labeling Changes

---

Please find attached the Division's labeling edits for NDA 205834. A word copy of the label will be attached to this correspondence.

Please be prepared to discuss these labeling comments at the late cycle meeting on August 7, 2014.

We are providing this above information via e-mail for your convenience. Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

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Linda C. Onaga, MPH  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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LINDA C ONAGA  
07/28/2014



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE**

**NDA:** 205834  
**Drug:** ledipasvir/sofosbuvir FDC  
**Date:** August 6, 2014  
**To:** Michele Anderson, Associate Director, Regulatory Affairs  
**Sponsor:** Gilead Sciences, Inc.  
**Subject:** NDA 205834 Rationale for Proposed Labeling Changes

---

Please find attached the Division's labeling edits for NDA 205834. A word copy of the label will be attached to this correspondence.

Please be prepared to discuss these labeling comments at the late cycle meeting on August 7, 2014.

We are providing this above information via e-mail for your convenience. Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

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Linda C. Onaga, MPH  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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LINDA C ONAGA  
08/06/2014



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE**

**NDA:** 205834  
**Drug:** ledipasvir/sofosbuvir FDC  
**Date:** July 28, 2014  
**To:** Michele Anderson, Associate Director, Regulatory Affairs  
**Sponsor:** Gilead Sciences, Inc.  
**Subject:** NDA 205834 Updated LCM

---

Please find below comments for NDA 205834. In addition, please find attached an updated agenda for Thursday's Late Cycle Meeting.

Due to increased tenofovir exposures observed with LDV/SOF + Atripla co-administration, safety assessment in HCV infected subjects receiving this combination is important to inform labeling decisions. Therefore, we request the following information:

- GS-US-337-0115 additional safety data with median 12 week duration of study drug exposure, in a similar format to that provided in SN 24 (SDN 26)
- NIAID-13-I-0159:
  - Assessment of (1) hypophosphatemia and (2) increased creatinine, including breakdown by antiretroviral treatment regimen and if these laboratory changes occurred in the same subjects.
  - Similar to the prior -0115 safety assessment, identification of any subjects with:
    - treatment emergent normoglycemic glycosuria
    - eGFR <50 mL/min
    - $\geq 25\%$  reduction in eGFR from baseline

We are providing this above information via e-mail for your convenience. Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

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Linda C. Onaga, MPH  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

## UPDATED LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** August 7, 2014 1:30 PM – 3:00 PM EST  
**Meeting Location:** Teleconference

**Application Number:** NDA 205834  
**Product Name:** ledipasvir/sofosbuvir fixed dose combination tablet  
**Indication:** treatment of genotype 1 chronic hepatitis C virus infection  
**Sponsor/Applicant Name:** Gilead Sciences, Inc.

### INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and cross-discipline team leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

### Discipline Review Letters

No Discipline Review letters have been issued to date.

### Substantive Review Issues

At this time we do not have any substantive review issues. However, if we learn of any issues from the outstanding CMC inspections, then the agenda will be modified accordingly.

### ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

### REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

### LCM AGENDA

1. Introductory Comments – Linda C. Onaga, MPH/Kimberly Struble, PharmD

Welcome, Introductions, Objectives of the meeting

2. Postmarketing Requirements/Postmarketing Commitments – 15 minutes

- Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response of ledipasvir/sofosbuvir in pediatric subjects 3 through 17 years of age with chronic hepatitis C.
- Collect long-term safety data for subjects enrolled in the pediatric ledipasvir/sofosbuvir safety, pharmacokinetic and efficacy study. Data collected should include at least 3 years of follow-up in order to characterize the long-term safety of ledipasvir/sofosbuvir including growth assessment, sexual maturation and characterization of ledipasvir/sofosbuvir resistance associated substitutions in viral isolates from subjects failing therapy.
- GS-US-337-0115 to provide safety data in HCV/HIV-1 subjects receiving concomitant tenofovir-containing regimens.
- GS-US-337-0123 to provide safety data in subjects with decompensated cirrhosis and/or in subjects receiving concomitant immunosuppressive agents (e.g., cyclosporine).
- Submit the final reports for the rat and mouse LDV carcinogenicity studies.
- The phenotypic assessment of NS5B\_A112T, NS5B\_E237G, and NS5B\_S473T in the HCV GT1a replicon.
- The longitudinal data on persistence of NS5A resistance substitutions from subjects who did not achieve SVR12 in the Phase 2 and 3 LDV/SOF studies in Sequence Registry Study GS-US-248-0122 and from subjects who did not achieve SVR12 in Phase 2 studies of LDV with other DAAs.

3. Major labeling issues –30 minutes

Please refer to your August 2, 2014, email containing the annotated label in response to the Division's comments dated July 28, 2014. Based on your responses we are modifying the labeling discussion. In general we agree with your proposed changes with the following exceptions to be discussed on August 7, 2014.

Section 2.1 Recommended Dose in Adults

The text should read "The recommended dose of [TRADENAME]..." The term dose is a single administration of a drug, whereas, the term dosage is a dosing regimen (one or more doses).

## Section 5.1 P-gp Inducers [REDACTED] (b) (4)

We recommend “e.g” is retained in the statement: P-gp inducers (e.g., rifampin or St. John’s wort)...

This comment also applies to section 7

## Section 5.2 [REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED]

## Section 7: Drug Interactions

We agree with your clinical comment for H2-receptor antagonists  
We are deferring labeling recommendations for use with tenofovir (see comments above).

## Section 12.3 [REDACTED] (b) (4)

[REDACTED] (b) (4)

We agree with the proposed inclusion of [REDACTED] (b) (4) data.

## Section 12.4: Microbiology

Minor edits were made to this section and are forthcoming. Additionally, statements regarding treatment-emergent NS5B substitutions were also added.

## Section 14: Clinical Studies

We agree with including the SVR12 rates from the 8 and 12 week treatment arms in subjects with baseline HCV RNA < 6 million IU/mL.

Please propose text to discuss the concordance between SVR12 and SVR24 data from ION-2.

4. Review Plans – 10 minutes
  - Finalize LDV/SOF labeling
  - Await facility inspection reports
5. Wrap-up and Action Items – 5 minutes



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/s/  
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LINDA C ONAGA  
08/05/2014



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE**

**NDA:** 205834  
**Drug:** ledipasvir/sofosbuvir FDC  
**Date:** July 14, 2014  
**To:** Michele Anderson, Associate Director, Regulatory Affairs  
**Sponsor:** Gilead Sciences, Inc.  
**Subject:** NDA 205834

---

We have the following comments for NDA 205834 dated February 7, 2014.

We have reviewed the preliminary safety data in subjects taking Atripla or its components (EFV+FTC+TDF) from GS-US-337-0115. Please provide target dates when a report in a similar format would be available in subjects taking Atripla or its components for the following:

- Median duration of study drug exposure at 8 weeks
- Median duration of study drug exposure at 10 weeks
- Median duration of study drug exposure at 12 weeks

We are providing this above information via e-mail for your convenience. Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

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Linda C. Onaga, MPH  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/  
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LINDA C ONAGA  
07/14/2014



NDA 205834

## INFORMATION REQUEST

Gilead Sciences, Inc.  
Attention: Michele Anderson  
Associate Director, Regulatory Affairs  
333 Lakeside Drive  
Foster City, CA 94404

Dear Ms. Anderson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ledipasvir/sofosbuvir fixed dose combination tablet.

We are reviewing the chemistry, manufacturing and controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Given that the dissolution specifications (method and acceptance criterion) would allow up to about (b) (4) % of (b) (4) ledipasvir in some tablets when testing is conducted at (b) (4) (i.e., at Q-(b) (4) %), we request the inclusion of additional monitoring in the control strategy for amorphous content. We recommend adding one of these three approaches:
  - a) Test all tablet batches at release, and annually on stability, using the (b) (4) method..
  - b) Add (b) (4) testing of tablets when dissolution testing at (b) (4) is needed at release and stability testing.
  - c) Add (b) (4) testing of tablets when the mean percent dissolved is less than (b) (4) % at Stage (b) (4) at release and stability testing.

Provide the updated drug product specifications and stability protocol incorporating the option selected.

2. The proposed particle size acceptance criterion for the sofosbuvir component of NMT (b) (4) % for (b) (4) will pass batches that fail the similarity testing for dissolution. Therefore, to ensure consistent drug product quality, the sofosbuvir particle size (b) (4) should be (b) (4). For this purpose, provide particle size distribution (b) (4) of the batches listed on Table 5 (submission dated April 25, 2014).

3. We note that the label states “Dispense only in original container”. Given that dispensing of less than a month’s supply of tablets could occur in practice please clarify your thoughts on this matter.

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

*{See appended electronic signature page}*

Rapti D. Madurawe, Ph.D.  
Branch Chief, Branch V  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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RAPTI D MADURawe  
07/08/2014

**From:** Onaga, Linda  
**To:** [michele.anderson@gilead.com](mailto:michele.anderson@gilead.com)  
**Bcc:** [Connelly, Sarah](#)  
**Subject:** NDA 205834  
**Date:** Monday, June 30, 2014 10:58:00 AM

---

Good Morning Michele,

Please find below comments for NDA 205834. We request your response by Thursday July 3, 2014.

*Please submit your causality assessment between LDV/SOF and cholelithiasis and cholecystitis events, integrating pertinent preclinical findings and the case occurring in GS-US-337-0128 (Subject #7832-1020).*

Thanks

Linda

*Linda C. Onaga, MPH  
Senior Regulatory Project Manager  
Division of Antiviral Products (DAVP)  
FDA/CDER/OND/OAP  
White Oak Complex, Bldg 22, Rm 6321  
10903 New Hampshire Ave.  
Silver Spring, MD 20993  
Ph: 301.796.0759  
Fax: 301.796.9883  
Email: [linda.onaga@fda.hhs.gov](mailto:linda.onaga@fda.hhs.gov)*

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/s/  
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LINDA C ONAGA  
07/01/2014



**From:** Onaga, Linda  
**To:** [michele.anderson@gilead.com](mailto:michele.anderson@gilead.com)  
**Bcc:** [Connelly, Sarah](#)  
**Subject:** NDA 205834 Comments  
**Date:** Tuesday, July 01, 2014 8:58:00 AM

---

Good Morning Michele,

Please find attached comments for NDA 205834. Please respond by Thursday July 3, 2014.

*Please provide complete narrative information on GS-US-248-0120 subjects who experienced ALT or AST >3x ULN and bilirubin >2x ULN, including your assessment of these cases. From our review, these subjects are #2761-6380 and #5664-6364. In addition, please integrate any additional cases in GS-US-248-0131, GS-US-248-0132, GS-US-248-0121, GS-US-256-0124 and GS-US-256-0148 meeting these laboratory criteria into your response.*

Thanks

Linda

*Linda C. Onaga, MPH  
Senior Regulatory Project Manager  
Division of Antiviral Products (DAVP)  
FDA/CDER/OND/OAP  
White Oak Complex, Bldg 22, Rm 6321  
10903 New Hampshire Ave.  
Silver Spring, MD 20993  
Ph: 301.796.0759  
Fax: 301.796.9883  
Email: [linda.onaga@fda.hhs.gov](mailto:linda.onaga@fda.hhs.gov)*

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LINDA C ONAGA  
07/01/2014



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE**

**NDA:** 205834  
**Drug:** ledipasvir/sofosbuvir FDC  
**Date:** July 1, 2014  
**To:** Michele Anderson, Associate Director, Regulatory Affairs  
**Sponsor:** Gilead Sciences, Inc.  
**Subject:** NDA 205834 Rationale for Proposed Labeling Changes

---

Please find attached the Division's labeling edits for NDA 205834. A word copy of the label will be attached to this correspondence.

We request your response no later than July 8, 2014.

We are providing this above information via e-mail for your convenience. Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

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Linda C. Onaga, MPH  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

34 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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LINDA C ONAGA  
07/01/2014



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE**

**NDA:** 205834  
**Drug:** ledipasvir/sofosbuvir FDC  
**Date:** June 25, 2014  
**To:** Michele Anderson, Associate Director, Regulatory Affairs  
**Sponsor:** Gilead Sciences, Inc.  
**Subject:** NDA 205834

---

We have the following comments for NDA 205834 dated February 7, 2014.

1. Ledipasvir/sofosbuvir FDC increases tenofovir (TFV) AUC, Cmax, and Ctau by 98%, 79% and 163%, respectively, when coadministered with Atripla. Please provide safety data (including AE's and lab value data) from GS-US-337-0116 and other trials, if applicable, to support the safety of this magnitude of increase on TFV exposure. Please indicate the median duration of tenofovir exposure to support the long term coadministration of Ledipasvir/sofosbuvir and Atripla.
2. Does Gilead have any data on persistence of NS5A substitutions that emerged on LDV treatment in phase 2 studies?

Please respond no later than **July 1, 2014**.

We are providing this above information via e-mail for your convenience. Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

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Linda C. Onaga, MPH  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/  
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LINDA C ONAGA  
06/25/2014



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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE**

**NDA:** 205834  
**Drug:** ledipasvir/sofosbuvir FDC  
**Date:** June 16, 2014  
**To:** Michele Anderson, Associate Director, Regulatory Affairs  
**Sponsor:** Gilead Sciences, Inc.  
**Subject:** NDA 205834

---

We have the following comments for NDA 205834 dated February 7, 2014.

The Safety Update Report *Section 2.1.4.1 Study GS-US-337-0123 (SOLAR-1), Exposure* reports two subjects died in Cohort A and two subjects died in Cohort B; however, the four subjects listed in *Section 2.1.4.3.2 Deaths* comprise three subjects in Cohort A (Subject #0200-75243, #5969-75231, #6927-75149) and only one subject in Cohort B (Subject #1086-75511). Please clarify this apparent discrepancy. In addition, please provide Cohort and fibrosis/cirrhosis status (e.g., F0-F3, CPT B, etc.) for the four additional subjects who died as reported in the SUR narratives (after the SUR data cut). The subject numbers are:

#0200-75242  
#3055-75425  
#0451-75523  
#1516-75527

Please respond no later than **June 18, 2014**.

We are providing this above information via e-mail for your convenience. Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

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Linda C. Onaga, MPH  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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LINDA C ONAGA  
06/16/2014





DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 205834

INFORMATION REQUEST

Gilead Sciences, Inc.  
Attention: Michele Anderson  
Associate Director, Regulatory Affairs  
333 Lakeside Drive  
Foster City, CA 94404

Dear Ms. Anderson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ledipasvir/sofosbuvir fixed dose combination tablet.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response by June 30, 2014, in order to continue our evaluation of your NDA.

You state (P.3.4, page 25) that “based on clinical manufacturing experience and chemical testing results, intermediate materials including [REDACTED] (b) (4)

[REDACTED]” Please provide data to show that [REDACTED] (b) (4)

[REDACTED] (b) (4)

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

*{See appended electronic signature page}*

Rapti D. Madurawe, Ph.D.  
Branch Chief, Branch V  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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RAPTI D MADURawe  
06/13/2014



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE**

**NDA:** 205834  
**Drug:** ledipasvir/sofosbuvir FDC  
**Date:** June 12, 2014  
**To:** Michele Anderson, Associate Director, Regulatory Affairs  
**Sponsor:** Gilead Sciences, Inc.  
**Subject:** NDA 205834

---

We have the following comments for NDA 205834 dated February 7, 2014.

1. Regarding subject #0334-71474 with post-treatment acute hepatitis, please comment if electron microscopy was performed on the liver biopsy, and if so, provide the report and assessment.
2. Please provide additional information for subject #3055-75304 (Safety Update Report, GS-US-337-0123) who discontinued study treatment due to increased ALT and AST, including but not limited to: follow up HCV RNA, any changes to immunosuppression regimen, additional work up, your assessment of this case.

Please respond no later than **June 18, 2014**.

We are providing this above information via e-mail for your convenience. Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

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Linda C. Onaga, MPH  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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LINDA C ONAGA  
06/12/2014



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE**

**NDA:** 205834  
**Drug:** ledipasvir/sofosbuvir FDC  
**Date:** June 5, 2014  
**To:** Michele Anderson, Associate Director, Regulatory Affairs  
**Sponsor:** Gilead Sciences, Inc.  
**Subject:** NDA 205834 Rationale for Proposed Labeling Changes

---

Please find attached the Division's Rationale for proposed labeling changes for NDA 205834. A word copy of the label will be attached to this correspondence.

We request your response no later than June 19, 2014.

We are providing this above information via e-mail for your convenience. Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

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Linda C. Onaga, MPH  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

## Rationale for Proposed Labeling Changes

This correspondence provides our rationale for the proposed labeling changes and focuses on Dosage and Administration, Adverse Reactions and Clinical Studies. Comments on other sections to the label are forthcoming. Please note, the proposed labeling differs from the mid-cycle communication and is based on further analyses and discussion with senior management. Please provide your response and updated label by June 19, 2014.

### (1) Dosage and Administration/Clinical Trials

The rationale for each of the recommended treatment durations for the listed patient populations is outlined below. At this time, the review team does not believe the benefit-risk assessment supports a labeling recommendation for (b) (4)

#### a. Treatment-naïve without cirrhosis

##### 12 week duration

The SVR12 rates >93% across the ION-3 treatment arms are acknowledged. Our review also took into consideration the relapse rates ranging 4.2-5.1% in the 8 week arms versus 1.4% in the 12 week arm. Statistical analyses determined RBV did not affect SVR or relapse rates; therefore, the 8 week arms were pooled for subsequent post hoc exploratory analyses. The pooled 8 week versus 12 week analysis demonstrated a statistically significant lower relapse rate in the 12 week as shown in Table 1.

**Table 1: Comparison of Relapse Rates Between Different Treatment Durations in ION-3 (All Treated)**

	Proportion Difference in Relapse Rate	95% Exact CI <sup>1</sup>
<b>8-Week LDV/SOF vs. 12-Week LDV/SOF</b>	3.7%	(0.4%, 7.7%)
<b>Combination of 8-Week LDV/SOF and 8-Week LDV/SOF+RBV vs. 12-Week LDV/SOF</b>	3.3%	(0.2%, 6.0%)

<sup>1</sup>based on inverting a two-sided test

Additional considerations supporting DAVP's recommendation for the 12 week duration include the acceptable safety profile of LDV/SOF, optimizing treatment success with the first regimen and minimizing development of NS5A and/or NS5B substitutions which may negatively impact future retreatment options.

##### Relapse Rates for Selected Subgroups Table

No statistically significant interactions were identified between treatment duration and subgroups defined by subject demographics and baseline characteristics. As shown in Table 2, no relapse occurred in subjects with baseline HCV RNA <1.5 million IU/mL while a baseline HCV ≥6 million IU/mL was associated with 8.9% relapse in the pooled 8 week groups versus 1.2% in the

12 week group. The 6 million IU/mL cut off was chosen because this value represented the largest proportion difference between 8 and 12 weeks in the subjects with low and high baseline viral load. (b) (4)

**Table 2: Relapse Rates by Baseline Viral Load for 8-Week and 12-Week Regimens in ION-3 (All Treated)**

	<b>8-Week LDV/SOF &amp; LDV/SOF+RBV</b>	<b>12-Week LDV/SOF</b>	<b>Proportion Difference (95% Exact CI)<sup>1</sup></b>	<b>P-value for Interaction Based on Zelen's Test</b>
<b>Baseline viral load (IU/mL)</b>				
< 1 million	0% (0/99)	0% (0/51)	0% (-7.8%, 3.8%)	not significant
≥ 1 million	5.9% (20/339)	1.8% (3/165)	4.1% (0.2%, 7.5%)	
< 1.5 million	0% (0/114)	0% (0/60)	0% (-3.3%, 6.7%)	not significant
≥ 1.5 million	6.4% (20/315)	1.9% (3/156)	4.4% (0.3%, 8.1%)	
< 2 million	1.4% (2/146)	1.4% (1/72)	0% (-6.6%, 3.7%)	0.34
≥ 2 million	6.4% (18/283)	1.4% (2/144)	5.0% (0.9%, 8.8%)	
< 2.5 million	1.9% (3/160)	1.2% (1/83)	0.7% (-4.9%, 4.4%)	0.46
≥ 2.5 million	6.3% (17/269)	1.5% (2/133)	4.8% (0.5%, 8.8%)	
< 3 million	1.7% (3/179)	1.1% (1/94)	0.6% (-4.3%, 4.0%)	0.46
≥ 3 million	6.8% (17/250)	1.6% (2/122)	5.2% (0.6%, 9.4%)	
< 3.5 million	1.5% (3/195)	1.0% (1/98)	0.5% (-4.2%, 3.6%)	0.44
≥ 3.5 million	7.3% (17/234)	1.7% (2/118)	5.6% (0.7%, 10.1%)	
< 4 million	1.9% (4/213)	0.9% (1/107)	0.9% (-3.6%, 4.2%)	0.53
≥ 4 million	7.4% (16/216)	1.8% (2/109)	5.6% (0.4%, 10.3%)	
< 5 million	2.1% (5/243)	0.8% (1/123)	1.2% (-2.7%, 4.1%)	1.0
≥ 5 million	8.1% (15/186)	2.2% (2/93)	5.9% (-0.1%, 11.4%)	
< 6 million	1.9% (5/260)	1.5% (2/131)	0.4% (-3.7%, 3.2%)	0.20
≥ 6 million	8.9% (15/169)	1.2% (1/85)	7.7% (1.9%, 13.3%)	
< 7 million	2.8% (8/286)	1.4% (2/145)	1.4% (-2.3%, 4.3%)	0.55
≥ 7 million	8.4% (12/143)	1.4% (1/71)	7.0% (0.2%, 13.2%)	
< 8 million	3.6% (11/306)	1.3% (2/151)	2.3% (-1.4%, 5.4%)	1.0
≥ 8 million	7.3% (9/123)	1.5% (1/65)	5.8% (-2.3%, 12.4%)	
< 9 million	3.8% (12/318)	1.3% (2/158)	2.5% (-1.3%, 5.6%)	1.0
≥ 9 million	7.2% (8/111)	1.7% (1/58)	5.5% (-2.9%, 12.4%)	
< 10 million	3.6% (12/332)	1.2% (2/166)	2.4% (-1.2%, 5.3%)	1.0
≥ 10 million	8.3% (8/97)	2.0% (1/50)	6.2% (-3.1%, 13.9%)	

<sup>1</sup>based on inverting a two-sided test

Additional baseline factors of genotype 1 subtype, presence/absence of NS5A resistance associated variants and IL28B status are included in the proposed Table 6 of the package insert to convey relapse information for providers to consider for their patients.

#### **b. Treatment-naïve with cirrhosis**

**12 week duration with consideration for 24 week duration for patients with multiple baseline factors traditionally associated with a lower response to HCV treatment**

Although a single relapse occurred in the 12 week arms of ION-1, this subject had multiple negative baseline predictive factors: cirrhosis, IL28B TT, presence of baseline NS5A RAV, high BL HCV RNA. In the ION-1 12 week arms approximately 3% of subjects were cirrhotic, IL28B non-C/C with baseline HCV RNA  $\geq 6$  million IU/ml. It is anticipated that if LDV/SOF receives FDA approval, more treatment-naïve subjects with cirrhosis and other baseline factors traditionally associated with a lower response to HCV treatment will receive therapy. The consequences of HCV treatment failure in patients with cirrhosis include risk of progression to decompensation and hepatocellular carcinoma. Our recommendation to consider extending treatment duration to 24 weeks incorporates the ION-2 data, hence, the following statement was included.

“It is estimated that the relapse rate in treatment-naïve patients with cirrhosis, including those with multiple baseline factors traditionally associated with a lower response to HCV treatment, will approximate the observed relapse rate in treatment-experienced patients with cirrhosis.”

Additionally our recommendation to consider extending the treatment duration to 24 weeks includes the acceptable safety profile of LDV/SOF, optimizing treatment success with the first regimen and minimizing development of NS5A and/or NS5B substitutions which may negatively impact future retreatment options.

**c. Treatment-experienced without cirrhosis**

**12 week duration with consideration for 24 week duration for patients with multiple baseline factors traditionally associated with a lower response to HCV treatment**

In the ION-2 non-cirrhotic population, relapse only occurred in the LDV/SOF 12 week arm as shown in Table 3.

**Table 3: ION-2 SVR12 and Relapse Rates**

	LDV/SOF 12 Week	LDV/SOF+RBV 12 Week	LDV/SOF 24 Week	LDV/SOF+RBV 24 Week
<b>Overall</b>				
SVR12	102/109 (93.6%)	107/111 (96.4%)	108/109 (99.1%)	110/111 (99.1%)
Relapse	6.5% (7/108)	3.6% (4/111)	0% (0/109)	0% (0/110)
<b>Cirrhosis-Yes</b>				
SVR	19/22 (86.4%)	18/22 (81.8%)	22/22 (100.0%)	22/22 (100.0%)
Relapse	13.6% (3/22)	18.2% (4/22)	0% (0/22)	0% (0/22)
<b>Cirrhosis-No</b>				
SVR	83/87 (95.4%)	88/88 (100.0%)	85/86 (98.8%)	88/89 (98.9%)



Relapse	4.7% (4/86)	0% (0/88)	0% (0/86)	0% (0/88)
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These subjects all had presence of baseline NS5A resistance substitution(s) as shown in Table 4.

**Table 4: Relapse by Baseline NS5A Resistance-Associated Substitutions, Non-cirrhotic population (ION-2, FDA analysis)**

	No Cirrhosis		
	LDV/SOF 12 Week	LDV/SOF+RBV 12 Week	LDV/SOF 24 week
(+) BL NS5A Resistance-Associated Substitutions - % of Subjects	22% (19/87)	20% (18/89)	19% (16/86)
<b>Relapse Rate by</b>			
(+)BL NS5A Resistance-Associated Substitutions	21% (4/19)	0% (0/18)	0% (0/16)
(-)BL NS5A Resistance-Associated Substitutions	0% (0/68)	0% (0/70)	0%

NS5A Resistance-Associated Substitutions include any change at NS5A positions 24, 28, 30, 31, 58, 92 or 93.

Our recommendation to consider extending treatment duration to 24 weeks factors is based on the 5% relapse rate in the LDV/SOF 12 week arm in subjects with baseline NS5A resistance-associated substitutions, the acceptable safety profile of LDV/SOF, optimizing treatment success with the regimen of LDV/SOF especially for previous NS3/4A failures and minimizing development of NS5A and/or NS5B substitutions which may negatively impact future retreatment options.

#### **d. Treatment-experienced with cirrhosis**

##### **24 week duration**

The recommendation for the 24 week duration in treatment-experienced patients with cirrhosis is based upon the 13-18% relapse rate in the 12 week arms (Table 3) compared with no relapses occurring in the 24 week arms. Further analyses showed that, compared to the pooled 12-week arms, the relapse rate for the pooled 24-week groups was approximately 16% lower (95% CI: [6.5%, 29.8%]) in the cirrhotic subjects and only 2% lower (95% CI: [0.1%, 6.0%]) in the non-cirrhotic subjects. The two 95% CIs did not overlap.

The consequences of HCV treatment failure in patients with cirrhosis including risk of progression to decompensation and hepatocellular carcinoma, the acceptable safety profile of LDV/SOF, optimizing treatment success with the LDV/SOF regimen and minimizing development of NS5A and/or NS5B substitutions which may negatively impact future retreatment options are additional factors supporting the 24 week duration recommendation.

**Relapse Rates for Selected Subgroups Table**

No statistically significant interaction was identified between treatment duration and subgroups defined by subject demographics and baseline characteristics, except possibly for the subgroup defined by cirrhosis status as mentioned above. However, some patient subgroups such as those with presence of baseline NS5A resistance-associated substitutions and non-CC IL28B status may benefit from a longer duration of 24 weeks. Please consider proposing baseline HCV RNA cut off's for display in this table.

33 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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LINDA C ONAGA  
06/06/2014



NDA 205834

**MID-CYCLE COMMUNICATION**

Gilead Sciences, Inc.  
Attention: Michele Anderson  
Associate Director, Regulatory Affairs  
333 Lakeside Drive  
Foster City, CA 94404

Dear Ms. Anderson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ledipasvir/sofosbuvir fixed dose combination tablet.

We also refer to the teleconference between representatives of your firm and the FDA on May 21, 2014. The purpose of the teleconference was to provide an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Linda C. Onaga, MPH, Senior Regulatory Project Manager at (301) 796-0759 or the Division mainline at (301) 796-1500.

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:  
Mid-Cycle Communication

## MID-CYCLE COMMUNICATION

**Meeting Date and Time:** May 21, 2014 1:00 pm – 2:00 pm

**Application Number:** 205834

**Product Name:** ledipasvir/sofosbuvir fixed dose combination

**Indication:** [TRADENAME] is a fixed-dose combination of ledipasvir, a hepatitis C virus (HCV) NS5A inhibitor and sofosbuvir, an HCV nucleotide analog NS5B polymerase inhibitor and is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection

**Applicant Name:** Gilead Sciences, Inc.

**Meeting Chair:** Kimberly Struble, PharmD, CDTL

**Meeting Recorder:** Linda Onaga, MPH, RPM

### FDA ATTENDEES

1. Edward Cox, MD, MPH, Director, Office of Antimicrobial Products (OAP)
2. John Farley, MD, Deputy Director, OAP
3. David Roeder, MS, ADRA, OAP
4. Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
5. Jeffrey Murray, MD, MPH, Deputy Director, DAVP
6. Kimberly Struble, Pharm D, CDTL, DAVP
7. Sarah Connelly, MD, Clinical Reviewer, DAVP
8. Jenny Zheng, PhD, Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)
9. Jeffry Florian, PhD, Pharmacometrics Reviewer, OCP
10. Shirley Seo, PhD, Clinical Pharmacology Team Lead, OCP
11. Fraser Smith, PhD, Biometrics Reviewer, DAVP
12. Karen Qi, PhD, Biometrics Reviewer, DAVP
13. Chris Ellis, PhD, Pharmacology/Toxicology Reviewer, DAVP
14. Hanan Ghantous, PhD, DABT, Pharmacology/Toxicology Team Lead, DAVP
15. George Lunn, CMC Reviewer, Office of New Drug Quality Assessment (ONDQA)
16. Sandra Suarez-Sharp, PhD, ONDQA Biopharmaceutics Reviewer, ONDQA
17. Lisa Naeger, PhD, Virology Reviewer, DAVP
18. Jules O'Rear, PhD, Virology Team Lead, DAVP
19. Karen Winestock, Chief, Project Management Staff, DAVP
20. Linda Onaga, MPH, Regulatory Project Manager, DAVP
21. Kimberly Taylor, Operations Research Analyst, CDER

### EASTERN RESEARCH GROUP ATTENDEES

22. Christopher Sees

### APPLICANT ATTENDEES

1. John McHutchison, M.D., Executive Vice President, Liver Disease Therapeutics
2. Michele Anderson, Associate Director, Regulatory Affairs
3. Roy Bannister, Ph.D., DABT, Senior Director, Drug Safety Evaluation
4. Neby Bekele, Ph.D., Senior Director, Biostatistics
5. Diana Brainard, M.D., Senior Director, Liver Disease Therapeutics
6. Jennifer Huber, M.S., Senior Manager, Regulatory Affairs
7. Anita Mathias, Ph.D., Director, Clinical Pharmacology
8. Linda McBride, R.Ph., RAC, Associate Director, Regulatory Affairs (CMC)
9. Hongmei Mo, M.D., Director, Clinical Virology
10. Reza Oliyai, Ph.D., Vice President, Formulation and Process Development
11. Phil Pang, M.D., Ph.D., Director, Liver Disease Therapeutics
12. Mike Sobczyk, Senior Director, Compliance
13. Mani Subramanian M.D., Vice President, Liver Disease Therapeutics
14. Chin H. Tay, Ph.D., DABT, Director, Drug Safety Evaluation
15. Paul Tomkins, Ph.D., Senior Director, Regulatory Affairs
16. Sonja Tong, Director, Regulatory Affairs Labeling

## 1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

## 2.0 SIGNIFICANT ISSUES

The following topics were discussed:

### Clinical/Statistics/Virology:

1. The Division acknowledged the high sustained virologic response (SVR) rate across trials and agrees ribavirin (RBV) is not needed for this genotype 1(GT1) population.
2. Internal discussions are ongoing regarding optimizing treatment duration for the least amount of relapse and the consequence of developing resistance, while balancing safety with an extended duration.

The two populations include:

- Treatment-naïve non-cirrhotic population
  - Finalizing analyses regarding consideration for extending treatment to 12 weeks for subjects with high baseline HCV RNA

- Treatment-experienced population, examining 12 versus 24 weeks
  - Finalizing analyses

(b) (4)

3. Available efficacy data in genotype 3 subjects are limited, and we believe are not sufficient to base a labeling conclusion at the present time. This decision by the review team factored the considerations of LDV/SOF+RBV data coming from 26 subjects, the trial being at a single non-US center, and the SVR rate is comparable to the approved SOF+RBV 24 week SVR rate and raises questions regarding the contribution of LDV to the regimen.

Gilead has additional data on approximately 80 subjects which could support 12 week treatment duration. The data includes the results from patients who received 12 weeks of LDV/SOF with and without RBV. SVR4 on all patients and SVR12 data on some patients will be available in July 2014. Complete SVR12 data will be available in September 2014. The Division suggested

(b) (4)

prior to submitting this data. Gilead should expect an advice/information request communication and proposed labeling language within the next two weeks

### 3.0 INFORMATION REQUESTS

#### Clinical/Stats

1. Information Requested Dated May 9, 2014 – causality assessment of various events (cardiac, hypersensitivity reactions, angioedema, chest pain, falls and fracture, palpitations and arrhythmia and rash)
2. Information Requested Dated May 12, 2014 – ION-3 subject status for those not achieving SVR12 due to “other” reason than relapse or with visit pending

#### Pharmacology/Toxicology

3. Information Request Dated March 18 and 21, 2014 – Submit a draft study report for ocular phototoxicity assessment of LDV in LE rats and risk assessment of the potential for (b) (4) to contribute to ocular and/or dermal phototoxicity by July 3, 2014
  - The Division requested this report to be submitted earlier than July 3<sup>rd</sup> if possible.
  - Gilead can provide a draft copy of the report one two days prior to the requested date, but not earlier.

#### CMC/ONDQA Biopharmaceutics:

4. Information Request Dated May 16, 2014: Dissolution acceptance criteria

Clinical Pharmacology:

5. Information Request Dated May 16, 2014: Dosing recommendations for hepatic impairment; DDI recommendations for cyclosporine, HIV medications including TDV containing regimens, ATV/RTV and verapamil; and the rationale on the differences in males and females and its impact on DDI with LDV

**4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT**

1. There are no major safety concerns identified at this time and there is currently no need for a REMS
2. Comprehensive safety review of the 8, 12 and 24 week LDV/SOF durations are ongoing, including safety considerations (b) (4). You have received the recent IRs pertaining to our safety review. In addition, consultations have been placed to our colleagues in the Ophthalmology and Hematology Divisions regarding the preclinical ocular signal and development of Factor VIII inhibitor, respectively (b) (4) based upon review of these events is ongoing.
3. Discussion regarding how to present safety data in the treatment-emergent adverse event table in the PI is ongoing, examining all cause, all grade vs. related, Grade (b) (4)

**5.0 ADVISORY COMMITTEE MEETING**

1. There are no plans at this time for an advisory committee meeting.

**6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES**

1. PMR/PMC labeling discussion – on or before July 15, 2014
2. Late Cycle Meeting Background Package – on or before July 23, 2014
3. Late Cycle Meeting with Gilead – Proposed Date August 7, 2014
4. PDUFA V Action Date: October 10, 2014



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/s/  
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DEBRA B BIRNKRANT  
06/03/2014

## **Executive CAC**

**Date of Meeting: May 27, 2014**

Committee: Abigail Jacobs, Ph.D., OND-IO, Acting Chair  
Paul Brown, Ph.D., OND IO, Member  
Lynnda Reid, Ph.D., DBRUP, Alternate Member  
Hanan Ghantous, Ph.D., DABT, DAVP, Supervisor  
Christopher Ellis, Ph.D., DAVP, Presenting Reviewer

Author of Draft: Christopher Ellis

**The following information reflects a brief summary of the Committee discussion and its recommendations.**

**NDA #** 205,834 and 204,671

**Drug Name:** Sofosbuvir (SOF)

**Sponsor:** Gilead Sciences Inc.

### **Rat Carcinogenicity Study**

Five groups of Sprague Dawley rats (55/group) were administered either vehicle (95% PEG 400, 5% Tween 80), water or SOF at doses of 75, 250 or 750 mg/kg/day for ~89 weeks (all males and group 5 females) or for ~100 weeks (group 1-4 females) by oral gavage. SOF administration was halted early in Group 5 females since only 20 animals remained. All groups were sacrificed early, since male and female control groups reached the pre-specified minimal group survival criteria (20 animals) prior to 104 weeks, with males and females sacrificed at ~89 and 100 weeks, respectively. Although not statistically significant, a trend for a SOF-related decrease in survival was noted in females only. SOF-related findings were limited to a slightly higher incidence of various clinical signs. Based on statistical criteria for rare and common tumors, no significant SOF-related tumor findings were noted in male or female rats.

### **Mouse Carcinogenicity Study**

Five groups of CD-1 mice (60/group) were administered either vehicle (95% PEG 400, 5% Tween 80), water or SOF at doses of 60, 200 or 600 mg/kg/day for ~92 weeks (females) or 20, 60 or 200 mg/kg/day for ~97 weeks (males) by oral gavage. The low and mid doses in males differed from the doses previously recommended by the execCAC, which recommended doses of 40 and 80 mg/kg. All groups were sacrificed early since both male and female vehicle control groups reached the pre-specified minimal group survival criteria (20 animals) prior to 104 weeks. No significant SOF-related effects on survival were observed. In addition, no dose limiting toxicities were observed, with SOF-related findings limited to reduced body weight (from week 17 to 39 only) and a slight increase in the incidence and severity of papillary mineralization and/or necrosis in kidney in Group 5 females. Based on statistical criteria for rare and common tumors, no significant SOF-related tumor findings were noted in male or female mice. It was noted that control male mice treated with water had a much higher incidence of hepatocellular adenoma/carcinoma than the vehicle or drug treated groups. The reason for this was not clear.

## **Executive CAC Recommendations and Conclusions:**

Rat:

- The Committee concurred that the study was acceptable, noting prior Exec CAC concurrence with the protocol, even though the treatment duration of males in the study was suboptimal due to mortality in the control groups.
- The Committee concurred that there were no drug-related neoplasms in a study with suboptimal exposure duration in males.

Mouse:

- The Committee concurred that the study was acceptable, noting prior Exec CAC concurrence with the protocol. The Committee also notes that the study duration was suboptimal in males and females due to mortality in the control groups.
- The Committee concurred that there were no drug-related neoplasms in a study with suboptimal exposure duration.

Abigail Jacobs, Ph.D.  
Acting Chair, Executive CAC

cc:\

- /Division File, DAVP
- /Hanan Ghantous, Team leader, DAVP
- /Christopher Ellis, Reviewer, DAVP
- /Linda Onaga, RPM, DAVP
- /ASeifried, OND-IO

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/s/  
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ADELE S SEIFRIED  
05/28/2014

ABIGAIL C JACOBS  
05/28/2014

**CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC) REPORT  
AND  
FDA-CDER RODENT CARCINOGENICITY DATABASE FACTSHEET**

P/T REVIEWER(s):	Christopher Ellis
DATE:	May 27, 2014
NDA:	205,834 (also 204,671 PMR)
DRUG CODE#:	GS-7977 (PSI-7977)
CAS#:	1190307-88-0
DIVISION(s):	Division of Antiviral Products
DRUG NAME(s):	Sofosbuvir (SOF)
SPONSOR:	Gilead Sciences Inc.
LABORATORY:	BASi, 10424 Middle Mt. Vernon Road, Mt. Vernon, IN 47620
CARCINOGENICITY STUDY REPORT DATE:	September 30, 2013 (rat); September 26, 2013 (mouse)
THERAPEUTIC CATEGORY:	Treatment of chronic HCV infection
PHARMACOLOGICAL/ CHEMICAL CLASSIFICATION:	HCV nucleotide analog NS5B polymerase inhibitor
MUTAGENIC/GENOTOXIC (y/n/equivocal/na; assay):	No [evaluated w/ GS-9851 (stereoisomeric mixture containing 50% GS-7977) in Ames, <i>in vitro</i> human lymphocyte chromosome aberration & <i>in vivo</i> mouse micronucleus assays]

## **RAT CARCINOGENICITY STUDY :**

RAT STUDY DURATION (weeks): ~89 (♂); ~100 (♀)  
STUDY STARTING DATE: October 27, 2010  
STUDY ENDING DATE: September 30, 2013  
RAT STRAIN: Sprague Dawley (SD®)  
ROUTE: Oral gavage  
DOSING COMMENTS: Once daily dosing w/ 5 ml/kg in vehicle  
(95% PEG 400, 5% Tween 80); C1=vehicle;  
C2=water

NUMBER OF RATS (#/sex/group):

- Control-1 (C1): 55 (main), 7 (TK)
- Control-2 (C2): 55 (main), 5 (TK)
- Low Dose (LD): 55 (main), 14 (TK)
- Middle Dose (MD): 55 (main), 14 (TK)
- High Dose (HD): 55 (main), 14 (TK)

RAT DOSE LEVELS (mg/kg/day):

- Low Dose: 75
- Middle Dose: 250
- High Dose: 750 (dosing halted at ~89 wks in females)

BASIS FOR DOSES SELECTED (MTD; AUC ratio; saturation; maximum feasible):

High-dose selected (~1/3 lethal dose) based on a 90-Day oral toxicology study with GS-7977 (MTD >500 mg/kg) and a 7-Day oral toxicology study with GS-9851 (lethality at 2000 mg/kg).

PRIOR FDA DOSE CONCURRENCE (Div./CAC)? (y/n; Date): Yes, November 3, 2010

RAT CARCINOGENICITY (conclusion: negative; positive; MF; M; F): Negative

RAT TUMOR FINDINGS: Refer to sponsor tables below.

**Table 1: Summary of statistical analysis for selected tumor types in male rats administered GS-7977, vehicle or water for ~20 months**

Sex Organ	Tumor	R/C	Group					Dose Response
			Vehicle Control	Water Control	Low	Mid	High	
M PROSTATE GLAND	TOTAL EXAMINED		(N) 55	55	55	55	55	
	ADENOMA	C	(a) 3	0	2	0	4	
			(pVC)	0.2706	0.7084	1.0000	0.3623	0.4280
			(pWC)		0.2140	1.0000	0.0836	0.0340

(N) Number of animals examined

(a) Number of animals with tumor

R/C Spontaneous tumor incidence rate < 1% (R=Rare tumor) or ≥ 1% (C=Common tumor)

(pVC,pWC) P-Values for peto analysis including control (vehicle control and water control, respectively):

Listed under water control: 2-sided pairwise comparison of vehicle control and water control

Listed under individual treatment group: 1-sided pairwise comparison of control with treatment group

Listed under 'Dose Response': 1-sided trend test including control and active treatment groups

Statistical Significance: Rare tumor - p<0.025 (trend), p<0.05 (pairwise); Common tumor - p<0.005 (trend), p<0.01 (pairwise)

\* Statistically significant at the defined significance level

**Table 2: Summary of statistical analysis for selected tumor types in female rats administered GS-7977, vehicle or water for ~20 to 23 months**

Sex	Organ	Tumor	R/C	Group					Dose Response
				Vehicle Control	Water Control	Low	Mid	High	
F	ADRENAL GLANDS	TOTAL EXAMINED	(N) 55	55	55	55	54	55	
		PHEOCHROMOCYTOMA; BENIGN	(a) 6	1	6	2	0	0	
		(pVC)		0.1466	0.3996	0.8949	1.0000	0.9846	
		(pWC)			0.0161	0.4719	1.0000	0.7286	
		PHEOCHROMOCYTOMA; M/B/C	(a) 7	1	7	4	1		
		(pVC)		0.0679	0.3982	0.7276	0.9731	0.9579	
		(pWC)			0.0085*	0.1149	0.7778	0.4667	
	MAMMARY GLAND (REGION)	TOTAL EXAMINED	(N) 55	55	54	55	54		
		MAMMARYADENOCARCINOMA/CARCINOMA	(a) 5	12	4	10	6		
		(pVC)		0.0898	0.7225	0.0479	0.3440	0.0863	
		(pWC)			0.9877	0.4462	0.8243	0.6456	
	PITUITARY GLAND	TOTAL EXAMINED	(N) 54	53	53	54	54		
		ADENOMA	(a) 25	20	25	23	20		
		(pVC)		0.3526	0.1934	0.4189	0.3895	0.5297	
		(pWC)			0.0406	0.0783	0.1411	0.1784	
	THYROID GLAND (BOTH LOBES)	TOTAL EXAMINED	(N) 55	55	55	55	55		
		ADENOMA; C-CELL	(a) 9	10	15	15	8		
		(pVC)		1.0000	0.0522	0.0279	0.4374	0.3268	
		(pWC)			0.0935	0.0452	0.4396	0.3798	
		CARCINOMA/ADENOMA, C-CELL	(a) 9	13	15	15	8		
		(pVC)		0.4496	0.0522	0.0279	0.4374	0.3268	
		(pWC)			0.2497	0.1310	0.6956	0.6189	
	UTERUS	TOTAL EXAMINED	(N) 55	55	55	55	55		
		ADENOCARCINOMA; ENDOMETRIAL	(a) 0	0	0	1	2		
		(pVC)		1.0000	1.0000	0.4857	0.1803	0.0300	
		(pWC)				1.0000	0.5313	0.1701	0.0307

(N) Number of animals examined

(a) Number of animals with tumor

R/C Spontaneous tumor incidence rate < 1% (R=Rare tumor) or > 1% (C=Common tumor)

(pVC,pWC) P-Values for peto analysis including control (vehicle control and water control, respectively):

Listed under water control: 2-sided pairwise comparison of vehicle control and water control

Listed under individual treatment group: 1-sided pairwise comparison of control with treatment group

Listed under 'Dose Response': 1-sided trend test including control and active treatment groups

Statistical Significance: Rare tumor - p<0.025 (trend), p<0.05 (pairwise); Common tumor - p<0.005 (trend), p<0.01 (pairwise)

\* Statistically significant at the defined significance level

#### RAT STUDY COMMENTS:

- GS-7977-related findings limited to higher incidence of various clinical signs.
- GS-7977 administration halted early in HD females (only 20 animals remained).
- All groups sacrificed early, since male and female control groups reached the pre-specified minimal group survival criteria (20 animals) prior to 104 weeks.
- Despite the early sacrifice of all groups and a trend (not statistically significant) for drug-related mortality in females, the study appears to be acceptable.
- GS-331007 AUC<sub>0-24h</sub> values at the high dose level (on Day 180) are ≥8- and 10-fold higher in males and females, respectively, than clinical exposure levels.

## **MOUSE CARCINOGENICITY STUDY:**

MOUSE STUDY DURATION (weeks): ~97 (♂); ~92 (♀)  
STUDY STARTING DATE: November 19, 2010  
STUDY ENDING DATE: September 26, 2013  
MOUSE STRAIN: ICR (CD-1<sup>®</sup>)  
ROUTE: Oral gavage  
DOSING COMMENTS: Once daily dosing w/ 5 ml/kg in vehicle  
(95% PEG 400, 5% Tween 80); C1=vehicle;  
C2=water

NUMBER OF MICE (#/sex/group):  
- Control-1 (C1): 60 (main), 10 (TK)  
- Control-2 (C2): 60 (main), 10 (TK)  
- Low Dose (LD): 60 (main), 54 (TK)  
- Middle Dose (MD): 60 (main), 54 (TK)  
- High Dose (HD): 60 (main), 54 (TK)

MOUSE DOSE LEVELS (mg/kg/day):  
- Low Dose: 20 (♂), 60 (♀)  
- Middle Dose: 60 (♂), 200 (♀)  
- High Dose: 200 (♂), 600 (♀)

BASIS FOR DOSES SELECTED (MTD; AUC ratio; saturation; maximum feasible):

MTD (>10% reduction in BW gain) based on 3-month oral dose finding study.

Note: Low/mid dose selection for males differs from CAC recommendations (40 & 80 mg/kg). The sponsor apparently selected lower doses to limit the study to 4 total GS-7977 formulations (as opposed to 5) to help prevent potential dosing errors.

PRIOR FDA DOSE CONCURRENCE (Div./CAC)? (y/n; Date): Yes, November 3, 2010

MOUSE CARCINOGENICITY (conclusion: negative; positive; MF; M;F): Negative

MOUSE TUMOR FINDINGS: Refer to sponsor table below. Note: No p-values <0.05 occurred in females.



**Table 3: Summary of statistical analysis for selected tumor types in male mice administered GS-7977, vehicle or water for ~97 weeks**

Sex Organ	R/C	Tumor		Group					Dose Response
				Vehicle Control	Water Control	Low	Mid	High	
M LIVER	C	TOTAL EXAMINED	(N) 60	60	59	60	59		
		HEPATOCELLULAR ADENOMA	(a) 3	14	1	5	2		
			(pVC)	0.0183	0.9186	0.2392	0.8321	0.4803	
	C	HEPATOCELLULAR CARCINOMA	(a) 2	12	4	4	5		
			(pVC)	0.0128	0.2590	0.3441	0.1078	0.1767	
			(pWC)		0.8652	0.9476	0.9315	0.9560	
	C	CARCINOMA/ADENOMA, HEPATOCELLULAR	(a) 5	23	5	8	6		
			(pVC)	0.0009*	0.3499	0.1862	0.3541	0.3402	
			(pWC)		0.9973	0.9976	0.9995	0.9998	
SYSTEMIC NEOPLASMS	C	TOTAL EXAMINED	(N) 60	60	60	60	60		
		MALIGNANT LYMPHOMA	(a) 0	7	3	0	3		
			(pVC)	0.0186	0.0928	1.0000	0.1345	0.2177	
			(pWC)		0.7650	1.0000	0.9118	0.9520	

(N) Number of animals examined

(a) Number of animals with tumor

R/C Spontaneous tumor incidence rate < 1% (R=Rare tumor) or ≥ 1% (C=Common tumor)

(pVC,pWC) P-Values for peto analysis including control (vehicle control and water control, respectively):

Listed under water control: 2-sided pairwise comparison of vehicle control and water control

Listed under individual treatment group: 1-sided pairwise comparison of control with treatment group

Listed under 'Dose Response': 1-sided trend test including control and active treatment groups

Statistical Significance: Rare tumor - p<0.025 (trend), p<0.05 (pairwise); Common tumor - p<0.005 (trend), p<0.01 (pairwise)

\* Statistically significant at the defined significance level

#### MOUSE STUDY COMMENTS:

- GS-7977-related findings limited to reduced body weight (from week 17 to 39 only) and a slight increase in the incidence and severity of papillary mineralization and/or necrosis in kidney in HD females (versus vehicle control).
- No significant GS-7977-related effects on survival observed.
- All groups sacrificed early, since male and female vehicle control groups reached the pre-specified minimal group survival criteria (20 animals) prior to 104 weeks.
- Despite the early sacrifice of all groups, the study appears to be acceptable.
- GS-331007 AUC<sub>0-24h</sub> values at the high dose levels (on Day 178) are ≥4- and 17-fold higher in males and females, respectively, than clinical exposure levels.

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/s/  
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CHRISTOPHER E ELLIS  
05/28/2014

HANAN N GHANTOUS  
05/28/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Silver Spring, MD 20993

NDA 205834

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Gilead Sciences, Inc.  
333 Lakeside Drive  
Foster City, CA 94404

ATTENTION: Michele Anderson  
Associate Director, Regulatory Affairs

Dear Ms. Anderson:

Please refer to your New Drug Application (NDA) dated February 8, 2014, received February 10, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ledipasvir/Sofosbuvir Tablets, 90 mg/400 mg.

We also refer to your correspondence dated and received February 28, 2014, requesting review of your proposed proprietary name, Harvoni. We have completed our review of the proposed proprietary name Harvoni, and have concluded that this name is acceptable.

If **any** of the proposed product characteristics as stated in your February 28, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager Linda Onaga, at (301) 796-0759.

Sincerely,

*{See appended electronic signature page}*

Kellie A. Taylor, Pharm.D., MPH  
Deputy Director  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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AZEEM D CHAUDHRY  
05/02/2014

TODD D BRIDGES on behalf of KELLIE A TAYLOR  
05/02/2014



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE**

**NDA:** 205834  
**Drug:** ledipasvir/sofosbuvir FDC  
**Date:** May 19, 2014  
**To:** Michele Anderson, Associate Director, Regulatory Affairs  
**Sponsor:** Gilead Sciences, Inc.  
**Subject:** NDA 205834

---

We have the following comments for NDA 205834 dated February 7, 2014.

1. Sofosbuvir (SOF) AUC was increased by 2.3-fold and 2.5-fold in subjects with moderate and severe hepatic impairment as compared to subjects with normal hepatic function when SOF is not combined with ledipasvir (LDV). However, because combination with LDV results in a 2.5-fold increase in SOF AUC, SOF exposures could be up to 5-fold higher in subjects with moderate or severe hepatic impairment when administered as the SOF/LDV fixed dose combination (FDC) as compared to SOF administered alone in subjects with normal hepatic function, if it is assumed that the effect is additive. Please provide additional justification and relevant safety data to support your conclusion that SOF/LDV FDC can be safely administered to patients with any degree of hepatic impairment.
2. Please provide a rationale on why the observed effect of cyclosporine (CsA) on SOF concentrations is so different between healthy volunteers and HCV-infected subjects post-transplant. Because SOF exposure is higher when it is coadministered with LDV, it is uncertain if SOF exposure would be higher in HCV-infected patients post-transplant when coadministered CsA. Generally the effects may not be directly additive if they are through the same pathway. However, it seems that the effect of CsA cannot solely be explained by P-gp or BCRP inhibition.
3. Please provide a rationale for the differential effects of 2 potent P-gp inhibitors (verapamil and cyclosporine) on LDV PK.
4. Please propose a mechanism and/or rationale for the observed gender difference on LDV exposures and comment on whether this difference may lead to any differences when interpreting drug-drug interaction differences. Please note that the flat exposure-response

relationships for safety and efficacy that are observed at the proposed dose may not be sufficient to changes in LDV exposure from DDIs for both genders:

- a. Atripla reduced the AUC and Cmax of LDV about 34%. Please provide efficacy data to support that this magnitude of decrease on LDV exposure would not decrease the effectiveness of SOF/LDV FDC in both men or women. Please keep in mind that the exposure for LDV is highly variable and that the drug-drug interaction effect would further add to the variability.
- b. Atazanavir/ritonavir (ATV/RTV) or verapamil increased LDV AUC about 2-fold. Please provide safety data to support the coadministration of ATV/RTV or verapamil with SOF/LDV in both men and women.

Please respond no later than **May 27, 2014**.

We are providing this above information via e-mail for your convenience. Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

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Linda C. Onaga, MPH  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/  
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LINDA C ONAGA  
05/19/2014



NDA 205834

## INFORMATION REQUEST

Gilead Sciences, Inc.  
Attention: Michele Anderson  
Associate Director, Regulatory Affairs  
333 Lakeside Drive  
Foster City, CA 94404

Dear Ms. Anderson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ledipasvir/sofosbuvir fixed dose combination tablets, 90/400 mg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response by June 30, 2014, in order to continue our evaluation of your NDA.

1. The provided dissolution data do not support the proposed acceptance criteria of  $Q = \frac{(b)}{(4)}\%$  at  $\frac{(b)}{(4)}$  minutes for LDV and SOF and are not acceptable. Implement the following dissolution acceptance criteria for both components of your proposed product and provide the revised specifications table with the updated acceptance criteria for the dissolution test.
  - Acceptance criterion:  $Q = \frac{(b)}{(4)}\%$  in 20 min
2. The data you provided in terms of dissolution as a function of LDV  $\frac{(b)}{(4)}$  content indicate that with a dissolution acceptance limit of  $Q = \frac{(b)}{(4)}\%$  at 20 min, it would be possible to accept batches with a  $\frac{(b)}{(4)}$  content up to  $\frac{(b)}{(4)}\%$ . Therefore, to justify/support up to  $\frac{(b)}{(4)}\%$  LDV  $\frac{(b)}{(4)}$  content in the specifications of your proposed product, provide information on the effect of percent  $\frac{(b)}{(4)}$  on the systemic exposure of LDV in humans, if available. If this information is not available, alternatively we recommend that you implement the following additional dissolution acceptance criterion as the quality control limit for LDV  $\frac{(b)}{(4)}$  content:



- Mean dissolution of < (b) (4) % in 20 minutes; Stage (b) (4)

As the trigger limit for in lab testing of (b) (4) form by (b) (4) or other analytical methodology.

3. On a submission dated April 30, 2014, it is suggested that the failing of similarity in dissolution between the batches manufactured at (b) (4) vs. those manufactured at Gilead Ireland is due to variations on the process parameters and that this variation will be resolved by harmonizing the manufacturing process parameters. Provide a list of the manufacturing parameters that will be harmonized and the specification ranges.

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

*{See appended electronic signature page}*

Rapti D. Madurawe, Ph.D.  
Branch Chief, Branch V  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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RAPTI D MADURawe  
05/16/2014



NDA 205834

**METHODS VALIDATION  
MATERIALS RECEIVED**

Gilead Sciences  
Attention: Michele Anderson  
333 Lakeside Drive  
Foster City, CA 94404

Dear Michele Anderson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ledipasvir and Sofosbuvir Tablets, 90 mg and 400 mg and to our February 26, 2014, letter requesting sample materials for methods validation testing.

We acknowledge receipt on May 14, 2014, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Michael L. Trehy  
MVP Coordinator  
Division of Pharmaceutical Analysis  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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MICHAEL L TREHY  
05/15/2014



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE**

**NDA:** 205834  
**Drug:** ledipasvir/sofosbuvir FDC  
**Date:** May 12, 2014  
**To:** Michele Anderson, Associate Director, Regulatory Affairs  
**Sponsor:** Gilead Sciences, Inc.  
**Subject:** NDA 205834

---

We have the following comments for NDA 205834 dated February 7, 2014.

- (1) We request all available ION-3 (GS-US-337-0108) SVR data for subjects not achieving SVR12 due to "other" reason than relapse or with visit pending.

Based upon our analyses, these subjects are:

GS-US-337-0108-0331-73182  
GS-US-337-0108-0334-73160  
GS-US-337-0108-0521-73218  
GS-US-337-0108-2111-73245  
GS-US-337-0108-2186-73108  
GS-US-337-0108-2728-73199  
GS-US-337-0108-3054-73039  
GS-US-337-0108-3054-73575  
GS-US-337-0108-4238-73209  
GS-US-337-0108-4238-73583  
GS-US-337-0108-4435-73553  
GS-US-337-0108-5292-73057  
GS-US-337-0108-5847-73029  
GS-US-337-0108-5847-73062  
GS-US-337-0108-5847-73216

- (2) Please submit narrative information on subject GS-US-337-0102-1305-71820, integrating the occurrence of lipase elevations and clinical events (e.g., abdominal pain upper, hemorrhagic gastritis).

Please respond no later than May 23, 2014.

We are providing this above information via e-mail for your convenience. Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

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Linda C. Onaga, MPH  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/  
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LINDA C ONAGA  
05/12/2014



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE**

**NDA:** 205834  
**Drug:** ledipasvir/sofosbuvir FDC  
**Date:** May 9, 2014  
**To:** Michele Anderson, Associate Director, Regulatory Affairs  
**Sponsor:** Gilead Sciences, Inc.  
**Subject:** NDA 205834

---

We have the following comments for NDA 205834.

- (1) Please submit your causality assessment of the following adverse events in the ledipasvir/sofosbuvir clinical program, including pertinent events in phase 1 and 2 trials and with the individual ledipasvir and sofosbuvir products:
- Hypersensitivity reactions and related events
  - Angioedema, swollen tongue and related events
  - Chest pain, chest discomfort, non-cardiac chest pain, hypertension
  - Falls and fracture events associated with falls, motor vehicle/motorbike accidents
  - Palpitations and arrhythmia events
  - Rash events
- (2) Please submit narrative information for the report of squamous cell carcinoma occurring in subject #GS-US-337-0102-5852-71535.

Please respond within 2 weeks, no later than May 22, 2014.

We are providing this above information via e-mail for your convenience. Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

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Linda C. Onaga, MPH  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research



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/s/  
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LINDA C ONAGA  
05/09/2014



NDA 205834

**INFORMATION REQUEST**

Gilead Sciences, Inc.  
Attention: Michele Anderson  
Associate Director, Regulatory Affairs  
333 Lakeside Drive  
Foster City, CA 94404

Dear Ms. Anderson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ledipasvir/sofosbuvir fixed dose combination tablets, 90/400 mg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response by May 2, 2014, in order to continue our evaluation of your NDA.

1. In the (b) (4) step of the manufacture of ledipasvir (b) (4) the acceptance criterion for completion is NMT (b) (4) % combined (b) (4) relative to ledipasvir, i.e., the sum of the two (b) (4) intermediates (see 3.2.S.2.2, pages 6-7). Please provide a justification for not including (b) (4) in this acceptance criterion.
2. You describe Normal Operating Ranges (NORs) and Proven Acceptable Ranges (PARs) as well as target values for each section of the manufacturing process, i.e., drug substance (3.2.S.2.6, pages 109-125), (b) (4) (3.2.P.2.3, Tables 25 (page 58) and 28 (page 67)), and drug product (3.2.P.2.3). In each case please describe how your knowledge of the NOR and the PAR informs your control of the manufacturing process. Do the operators have freedom to move within the NOR and/or PAR in every case or only in certain circumstances?
3. In Section 3.2.P.3.2 you provide (b) (4)

4. Provide a detailed description of the (b) (4). Provide validation data and indicate the limits of detection.
5. Provide validation reports for methods (b) (4).
6. Add acceptance criteria for (b) (4).
7. Please confirm that you will not market any tablets made with sofosbuvir manufactured by (b) (4).
8. Add resolution as a system suitability test for HPLC method TM-215 and for the HPLC method used in the dissolution method TM-213.
9. Conduct photostability testing for tablets in the alternate trade dress and provide this information expeditiously. Please provide the 3 month stability test data for Batch DK1307B1 of tablets in the alternate trade dress as soon as they become available.
10. Section 3.2.P.3.4, 1.1.7.2, page 19 indicates a confirmatory study has been initiated in which tablets manufactured from (b) (4) that is (b) (4) months old are placed on stability (i.e., “end-to-end” stability) and monitored throughout their shelf life. Please submit this information to the Annual Report when it becomes available. Until the “end-to-end” stability data becomes available, please limit the (b) (4) storage period to that of the (b) (4) used in the clinical or primary stability batches.

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

*{See appended electronic signature page}*

Rapti D. Madurawe, Ph.D.  
Branch Chief, Branch V  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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RAPTI D MADURawe  
04/18/2014



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE**

**NDA:** 205834  
**Drug:** ledipasvir/sofosbuvir FDC  
**Date:** April 10, 2014  
**To:** Michele Anderson, Associate Director, Regulatory Affairs  
**Sponsor:** Gilead Sciences, Inc.  
**Subject:** NDA 205834

---

We have the following comments for NDA 205834 dated February 7, 2014.

1. Please provide a summary of all serious and/or  $\geq$ Grade 3 gastrointestinal events occurring in the LDV/SOF program, integrating pertinent preclinical findings and including an assessment of potential causality with LDV/SOF.
2. Please provide all follow up clinical information, including discharge summaries, on the following subjects:
  - a. Case #GS-US-337-0102-0334-71474, Acute Hepatitis
  - b. Case #GS-US-337-0102-5667-71227, Abdominal discomfort
  - c. Case #GS-US-337-0109-2493-79305, Hepatic Encephalopathy
  - d. Case #GS-US-337-0109-0521-79131, Transient Blindness

Please respond no later than May 2, 2014.

We are providing this above information via e-mail for your convenience. Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

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Linda C. Onaga, MPH  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/  
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LINDA C ONAGA  
04/10/2014



NDA 205834

**FILING COMMUNICATION –  
NO FILING REVIEW ISSUES IDENTIFIED**

Gilead Sciences, Inc.  
Attention: Michele Anderson  
Associate Director, Regulatory Affairs  
333 Lakeside Drive  
Foster City, CA 94404

Dear Ms. Anderson:

Please refer to your New Drug Application (NDA) dated February 7, 2014, received February 10, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for ledipasvir/sofosbuvir fixed dose combination tablet, 90 mg/400 mg.

We also refer to your amendments dated February 27, 2014, February 28, 2014, March 4, 2014, March 11, 2014, and March 13, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is October 10, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by July 15, 2014. In addition, the planned date for our internal mid-cycle review meeting is May 12, 2014. We are not currently planning to hold an advisory committee meeting to discuss this application.

## **PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

## **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission 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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

## **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.

We acknowledge receipt of your request for a partial waiver and a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

If you have any questions, call Linda C. Onaga, Senior Regulatory Project Manager, at (301) 796-0759 or (301) 796-1500.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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DEBRA B BIRNKRANT  
03/31/2014



NDA 205834

**INFORMATION REQUEST**

Gilead Sciences, Inc.  
Attention: Michele Anderson  
Associate Director, Regulatory Affairs  
333 Lakeside Drive  
Foster City, CA 94404

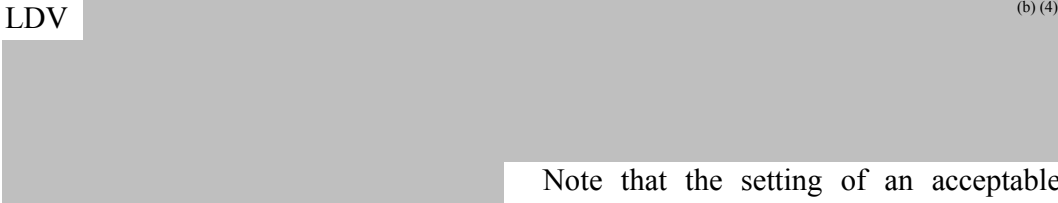
Dear Ms. Anderson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ledipasvir/sofosbuvir fixed dose combination tablets, 90/400 mg.

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a prompt written response by April 25, 2014, in order to continue our evaluation of your NDA.

1. To support the approval of the proposed dissolution method provide the following:
  - a. Confirm whether the proposed dissolution medium, 900 mL of 10 mM potassium phosphate, pH 6.0 with 1.5% polysorbate 80 and 0.0075 mg/mL BHT, was used to assess the dissolution profiles of the pivotal clinical batches, registration stability and commercial batches.
  - b. A list of the Critical Material Attributes (CMA) and Critical Process Parameters (CPP) affecting dissolution with supporting data.
  - c. Dissolution profiles for both LDV and SOF as a function of drug substance particle size, (b) (4) and other relevant attributes.
  - d. (b) (4) However, data supporting the discriminating ability of the dissolution method for these potential changes were not included in your submission. Provide rationale with supporting data.
2. Provide an explanation for the outlier behavior on the SOF dissolution profile for Batch DK1206B manufactured at (b) (4). Please include in your explanation the drug substance

particle size, (b) (4) and in process parameters operating ranges for this batch.

3. To support the use of dissolution as a tool to monitor for LDV (b) (4) content provide:
  - a. Data showing that the proposed dissolution method is able to reject batches with LDV (b) (4)  
  
Note that the setting of an acceptable specification limit of morphic form can be supported by clinical information (i.e., bioavailability, exposure-response, etc.).
4. To support the approval of the alternate manufacturing site provide:
  - a. Dissolution profiles comparisons in three different media for the batches (at least 3) manufactured at (b) (4) vs. those manufactured at Gilead in Ireland.
5. Although the detailed CMC information for sofosbuvir drug substance is referenced to NDA 204-671, Module 3 should also include a drug substance section (i.e., 3.2.S) for sofosbuvir. Include in Module 3 of NDA 205-834 the current information on sofosbuvir drug substance (such as manufacturers, physico-chemical properties, specification, storage condition and retest date, etc.), as well as a discussion of attributes of sofosbuvir drug substance that are important for the manufacture and quality of the ledipasvir and sofosbuvir tablet.
6. Provide a Letter of Authorization to allow FDA to reference all information in NDA 204-671.
7. Provide one bottle each of the US (active) tablets, and the Access (active) tablets. We wish to examine the tablets and the bottles, so container labels or induction seals are not necessary. If supplies are tight a sample of 10 tablets of each type in an appropriate container is sufficient.

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.  
Branch Chief, Branch V  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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RAPTI D MADURawe  
03/21/2014



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE**

**NDA:** 205834  
**Drug:** ledipasvir/sofosbuvir FDC  
**Date:** March 21, 2014  
**To:** Michele Anderson, Associate Director, Regulatory Affairs  
**Sponsor:** Gilead Sciences, Inc.  
**Subject:** NDA 205834

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We have the following comments for NDA 205834 dated March 13, 2014.

Please provide a risk assessment of the potential for (b) (4) to contribute to ocular and dermal phototoxicity, addressing its absorption of visible and UV light, whether it has the potential for photo-crosslinking to cellular macromolecules, and its generation from LDV by photolysis. Based on this assessment, you may want to consider using an LDV batch with a relatively high percentage of (b) (4) in your planned ocular phototoxicity study in Long Evans rats.

We are providing this above information via e-mail for your convenience. Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

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Linda C. Onaga, MPH  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/  
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LINDA C ONAGA  
03/21/2014





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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE**

**NDA:** 205834  
**Drug:** ledipasvir/sofosbuvir FDC  
**Date:** March 18, 2014  
**To:** Michele Anderson, Associate Director, Regulatory Affairs  
**Sponsor:** Gilead Sciences, Inc.  
**Subject:** NDA 205834

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We have the following comments for NDA 205834 dated March 13, 2014.

We acknowledge your recent response and consider your proposed alternative approach (as outlined in paragraph 3) acceptable. We recommend including TK assessment (unless data available from previous studies) and selecting a high dose level that is able to achieve a reasonable clinical exposure multiple (*e.g.* 10-fold). In addition, we acknowledge your intention to submit a draft report to the NDA no later than July 3<sup>rd</sup>. Please also note that efforts to submit this report in advance of this July 3<sup>rd</sup> date would be appreciated greatly (to allow additional time for Agency review).

We are providing this above information via e-mail for your convenience. Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

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Linda C. Onaga, MPH  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/  
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LINDA C ONAGA  
03/18/2014



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE**

**NDA:** 205834  
**Drug:** ledipasvir/sofosbuvir FDC  
**Date:** March 12, 2014  
**To:** Michele Anderson, Associate Director, Regulatory Affairs  
**Sponsor:** Gilead Sciences, Inc.  
**Subject:** NDA 205834

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We have the following comments for NDA 205834 dated February 10, 2014.

Please ensure a summary of all cases of myocardial ischemia are included in the NDA 205834 safety update report.

We are providing this above information via e-mail for your convenience. Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

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Linda C. Onaga, MPH  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/  
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LINDA C ONAGA  
03/12/2014



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE**

**NDA:** 205834  
**Drug:** ledipasvir/sofosbuvir FDC  
**Date:** March 07, 2014  
**To:** Michele Anderson, Associate Director, Regulatory Affairs  
**Sponsor:** Gilead Sciences, Inc.  
**Subject:** NDA 205834 SDN #3; phototoxicity comments (SN 001, dated 02/27/14)

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After considering your response and available LDV data, it is our contention that significant uncertainty regarding the potential for ocular phototoxicity with LDV exists. Thus, we are not convinced that available data provide an adequate assessment of ocular phototoxicity risk and believe this risk should be further evaluated. Therefore, please conduct an in-vitro 3T3 NRU phototoxicity test with LDV and submit this data to the NDA by July 3<sup>rd</sup>. Please note that given the time constraints a draft report would be acceptable.

**Please respond by March 14, 2014.**

We are providing this above information via e-mail for your convenience. Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

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Linda C. Onaga, MPH  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/  
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SOHAIL MOSADDEGH  
03/07/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 205834

**PROPRIETARY NAME  
ACKNOWLEDGEMENT**

Gilead Sciences, Inc.  
333 Lakeside Drive  
Foster City, CA 94404

ATTENTION: Michele Anderson  
Associate Director, Regulatory Affairs

Dear Ms. Anderson:

Please refer to your New Drug Application (NDA) dated February 8, 2014, received February 10, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sofosbuvir/Ledipasvir Tablets, 400 mg/90 mg.

We also refer to your correspondence dated and received February 28, 2014, requesting a review of your proposed proprietary name, Harvoni. Upon preliminary review of your submission, we have determined that it is a complete submission as described in our Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*.

If the application is filed, the user fee goal date is May 29, 2014.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application, contact Linda Onaga, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0759.

Sincerely,

*{See appended electronic signature page}*

Danyal Chaudhry, M.P.H.  
Safety Regulatory Project Manager  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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AZEEM D CHAUDHRY  
03/04/2014





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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE**

**NDA:** 205834  
**Drug:** ledipasvir/sofosbuvir FDC  
**Date:** February 28/, 2014  
**To:** Michele Anderson, Associate Director, Regulatory Affairs  
**Sponsor:** Gilead Sciences, Inc.  
**Subject:** NDA 205834

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You propose to perform reduced Microbial Limits testing for drug product release. Microbial limits testing may be omitted from the product release specification provided adequate (b) (4) microbiological controls are established and documented. If you wish to omit the microbial limits specification, more information on your process is requested. Address the following points.

1. Identify and justify critical control points in the drug product manufacturing process that could affect the microbial load of the drug product. Please consider all active pharmaceutical ingredients as well as excipients. Comment on potential differences in microbial control at all manufacturing locations. Also describe any risk assessment studies or hold time studies (i.e., for the tablet coating solution) that have been performed that would support your proposal for reduced microbial limits testing.
2. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods for your drug product. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.
3. Describe activities taken when microbiological acceptance criteria are not met at control points.

In addition to these points, address the following:

1. Provide the results of microbial limits testing performed on exhibit or stability batches of the drug product at all manufacturing locations, or provide justification as to why limited information is provided.
2. In the absence of historical data for all facilities, you should perform quarterly microbial limits testing on stability batches for the first year of stability. Following the first year, testing may be performed annually.

3. Include annual microbial limits testing in the post approval commitment.

4. (b) (4)  
Without additional information, the former would be a better indicator of the potential for microbial growth.

**Please respond by April 11, 2014.**

We are providing this above information via e-mail for your convenience. Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

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Linda C. Onaga, MPH  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/  
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LINDA C ONAGA  
02/28/2014



NDA 205834

**REQUEST FOR METHODS  
VALIDATION MATERIALS**

Gilead Sciences  
Attention: Michele Anderson  
333 Lakeside Drive  
Foster City, CA 94404

Dear Michele Anderson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ledipasvir and Sofosbuvir tablets, 90 mg and 400 mg.

We will be performing methods validation studies on Ledipasvir and Sofosbuvir tablets, 90 mg and 400 mg, as described in NDA 205834.

In order to perform the necessary testing, we request the following sample materials and equipments:

**Method, current version**

TM-216.01 Identification, Assay, and Impurity Content of Ledipasvir (b) (4)

Drug Substance by HPLC

TM-214 Identification, Strength, and Degradation Product Content of Ledipasvir and Sofosbuvir Tablets by UPLC

**Samples and Reference Standards**

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

60 Ledipasvir and Sofosbuvir tablets, 90 mg and 400 mg

**Equipment**

[REDACTED] (b) (4)  
[REDACTED]  
[REDACTED]

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration  
Division of Pharmaceutical Analysis  
Attn: MVP Sample Custodian  
645 S Newstead  
St. Louis, MO 63110

Please notify me upon receipt of this letter. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Michael L. Trehy, Ph.D.  
MVP coordinator  
Division of Pharmaceutical Analysis  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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MICHAEL L TREHY  
02/26/2014



NDA 205834

## NDA ACKNOWLEDGMENT

Gilead Sciences, Inc.  
Attention: Michele Anderson  
Associate Director, Regulatory Affairs  
333 Lakeside Drive  
Foster City, CA 94404

Dear Ms. Anderson:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: ledipasvir/sofosbuvir fixed dose combination tablets, 90/400 mg

Date of Application: February 8, 2014

Date of Receipt: February 10, 2014

Our Reference Number: NDA 205834

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 11, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Antiviral Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Linda C. Onaga, MPH, Regulatory Project Manager, at (301) 796-0759 or (301) 796-1500.

Sincerely,

*{See appended electronic signature page}*

Linda C. Onaga, MPH  
Senior Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research



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/s/  
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LINDA C ONAGA  
02/19/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 115268

**MEETING MINUTES**

Gilead Sciences, Inc.  
Attention: Michele Anderson  
Associate Director, Regulatory Affairs  
333 Lakeside Drive  
Foster City, CA 94404

Dear Ms. Anderson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ledipasvir/sofosbuvir fixed dose combination tablet.

We also refer to the telecon between representatives of your firm and the FDA on January 27, 2014. The purpose of the meeting was to discuss SVR12 data for three Phase 3 studies, ION-1, ION-2, and ION-3 that will be used to support a new drug application (NDA) for ledipasvir/sofosbuvir fixed dose combination tablet.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Linda C. Onaga, MPH, Regulatory Project Manager at (301) 796-0759 or (301) 796-1500.

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:  
Meeting Minutes

IND 115268  
Meeting Minutes  
Type C  
OAP/DAVP

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type C  
**Meeting Category:** Guidance

**Meeting Date and Time:** January 21, 2014 2:00 PM – 3:30 PM  
**Meeting Location:** 10903 New Hampshire Ave  
White Oak Building 22, Conference Room 1421  
Silver Spring, MD 20903

**Application Number:** 115268  
**Product Name:** ledipasvir/sofosbuvir fixed dose combination tablet  
**Proposed Indication:** treatment of genotype 1 chronic hepatitis C (CHC) infection in adults  
**Sponsor/Applicant Name:** Gilead Sciences, Inc.

**Meeting Chair:** Debra Birnkrant, MD  
**Meeting Recorder:** Linda C. Onaga, MPH

### FDA ATTENDEES

1. Debra Birnkrant, M.D., Director, Division of Antiviral Products (DAVP)
2. Jeffrey Murray, M.D., M.P.H., Deputy Director, DAVP
3. Sarah Connelly, M.D., Clinical Reviewer, DAVP
4. Kimberly Struble, Pharm.D., Clinical Team Leader, DAVP
5. Christopher Ellis, Ph.D., Pharmacology/Toxicology Reviewer, DAVP
6. Lisa Naeger, Ph.D., Clinical Virology Reviewer, DAVP
7. Eric Donaldson, Ph.D., Clinical Virology Reviewer, DAVP
8. Jules O'Rear, Ph.D., Clinical Virology Team Leader, DAVP
9. Leslie Chinn, Ph.D., Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)
10. Stanley Au, Ph.D., Clinical Pharmacology Reviewer, OCP
11. Jeffry Florian, Ph.D., Pharmacometrics Reviewer, OCP
12. Karen Qi, Ph.D., Biometrics Reviewer, Division of Biometrics IV (DBIV)
13. Fraser Smith, Ph.D., Secondary Biometrics Reviewer, DBIV
14. Karen Winestock, Chief, Project Management Staff, DAVP
15. Linda C. Onaga, M.P.H., Regulatory Project Manager, DAVP

### SPONSOR ATTENDEES

1. Michele Anderson, Associate Director, Regulatory Affairs
2. Neby Bekele, PhD, Senior Director, Biostatistics
3. Anita Mathias, PhD, Director, Clinical Pharmacology

4. John McHutchison, MD, Executive Vice President, Liver Disease Therapeutics
5. Jennifer Huber, MS, Senior Manager, Regulatory Affairs
6. Linda McBride, Associate Director, Regulatory Affairs CMC
7. Hongmei Mo, MD, Director, Clinical Virology
8. Reza Oliyai, PhD, Vice President, Formulation and Process Development
9. Phil Pang, MD, PhD, Director, Liver Disease Therapeutics
10. William T. Symonds, Pharm D, Vice President, Liver Disease Therapeutics
11. Chin Tay, PhD, DABT, Director, Drug Safety Evaluation (Toxicology)
12. Taiyin Yang, PhD, Senior Vice President, Pharmaceutical Development and Manufacturing

## **1.0 BACKGROUND**

Gilead Sciences, Inc. is developing ledipasvir/sofosbuvir (LDV/SOF) fixed dose combination tablet for the treatment of genotype 1 chronic hepatitis C virus infection in adults. Sofosbuvir is an approved nucleotide NS5B polymerase inhibitor and ledipasvir is an NS5A inhibitor. The Division of Antiviral Products granted Breakthrough Therapy Designation for this fixed dose combination on July 22, 2013.

Gilead requested a Type C Guidance meeting with the Division of Antiviral Products to discuss SVR12 data for the Phase 3 studies ION-1, ION-2, and ION-3, which will support the LDV/SOF new drug application. The trials, ION-1 (GS-US-337-0102), ION-2 (GS-US-337-0109), and ION-3 (GS-US-337-0108) are multicenter, randomized, open-label studies to investigate the efficacy and safety of LDV/SOF FDC with or without ribavirin in genotype 1, HCV-infected subjects. ION-1 and ION-2 are evaluating the fixed-dose combination of LDV/SOF with or without ribavirin (RBV) for 12 or 24 weeks in treatment-naïve subjects and treatment-experienced subjects, respectively. ION-3 is evaluating the fixed dose combination of LDV/SOF for 12 weeks and LDV/SOF ± RBV for 8 weeks in treatment-naïve, non-cirrhotic subjects.

The purpose of this meeting is to discuss the Phase 3 clinical data and seek agreement on the data that will support an indication for the use of LDV/SOF FDC for the treatment of genotype 1 chronic HCV infection in adults.

Note: This Type C meeting was originally scheduled for January 21, 2014. The Federal Government closed on January 21, 2014 due to inclement weather and the meeting was rescheduled for January 27, 2014 as a teleconference.

## **2.0 DISCUSSION**

Gilead will provide a written response to the Agency's additional comments after this meeting. Also, Gilead intends to submit the original NDA for the ledipasvir/sofosbuvir fixed dose combination tablet the week of February 10, 2014.

## 2.1. FDA Additional Comments

**FDA Additional Comment 1:** *We note relapse only occurred in the 12 week arms of ION-2, with numerically lower relapse rates in the 12 week ribavirin-containing arm. The Type C meeting backgrounder indicates cirrhosis is the only factor identified as a predictor of relapse in multivariate analysis.* (b) (4)

**FDA Additional Comment 2:** *Higher relapse rates are noted in the 8 week arms compared with the 12 week arm of ION-3. The NDA submission should contain sufficient information to support your rationale* (b) (4)

### **Discussion(1 and 2):**

Gilead will provide rationales (b) (4)

in the original NDA submission. Gilead noted (b) (4)

**FDA Additional Comment 3:** *In the NDA, please include an assessment across trials of the impact of each NS5A resistance substitution on achieving SVR, including an assessment of the percentage of resistant variants and copies/mL at baseline by next generation sequencing and effect on the SVR rate (see Gilead publication by Goodman et al., 2011).*

### **Discussion:**

Gilead will provide an analysis of the impact of NS5A resistance substitution across the Phase 2 and 3 trials in the original NDA submissions. Additional analyses on the impact of individual and group of mutations (by EC<sub>50</sub> value shift) and mutation viral load will also be included. Gilead agreed to review and include in the original NDA an analysis of the NS5A RAVs by geographic region and the frequency of NS5A RAVs in the U.S. population.

**FDA Additional Comment 4:** *Please provide an update regarding how much data on prior SOF-failures and prior LDV/SOF-failures will be included at NDA submission. In the NDA, please provide a summary report of all subjects retreated with LDV+SOF regimens after failure on SOF and LDV/SOF regimens and include all resistance information on these subjects.*

### **Discussion:**

Gilead will provide data on 20 subjects who experienced virologic failure after prior treatment with a SOF-based therapy in the original NDA. Additional data (SVR4) from GS-US-337-1118, an ongoing trial including prior SOF-based treatment failure subjects, will be available in July 2014.

**FDA Additional Comment 5:** *We acknowledge the anticipated availability of an interim SOLAR-1 clinical study report during the review of the NDA* (b) (4)

**Discussion:**

Gilead will submit interim clinical study report for SOLAR-1 in July 2014 to IND 115268. This study report will include SVR 12 data in approximately 80 subjects who received 12 weeks of treatment with the LDV/SOF FDC with ribavirin.

**FDA Additional Comment 6:** *We remind you of our prior pre-NDA comment: We recommend the established names be ordered alphabetically, as we have been recommending for HIV drugs. e.g., "Ledipasvir and Sofosbuvir". A main consideration is the number of pharmacological mechanisms for HCV and HIV drugs, which makes mechanism-based ordering very complicated.*

**Discussion:**

Gilead will update the FDC nomenclature according to the Agency guidance as stated in the pre-NDA meeting (ledipasvir/sofosbuvir). Labeling will reflect the alphabetical order, however, certain sections of the original NDA will not reflect the change.

**FDA Additional Comment 7:** *Please provide any updated plans for use of LDV/SOF FDC via expanded access/treatment IND, EIND or single-patient IND.*

**Discussion:**

SOLAR-1 and SOLAR-2 provide treatment for patients with the greatest need. There are approximately 700 subjects enrolled in both studies combined, with SOLAR-1 fully enrolled. SOLAR-1 has 27 sites in the US. Child C post-transplant subjects are low in enrollment. Gilead has not received EIND requests for the FDC, however, they are committed to providing the FDC through single-patient or emergency INDs.

**Advisory Committee (AC) Meeting Discussion**

Gilead asked whether an AC meeting will be scheduled. The FDA stated that at this time an AC meeting will not be needed, but if something arises during the review of the NDA, an AC meeting might be needed.

### **3.0 PREA REQUIREMENTS**

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov). For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

### **4.0 ISSUES REQUIRING FURTHER DISCUSSION**

None.

### **5.0 ATTACHMENTS AND HANDOUTS**

None.

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/s/  
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DEBRA B BIRNKRANT  
02/14/2014



**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



NDA 205834

**LATE-CYCLE MEETING MINUTES**

Gilead Sciences, Inc.  
Attention: Michele Anderson  
Associate Director, Regulatory Affairs  
333 Lakeside Drive  
Foster City, CA 94404

Dear Ms. Anderson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ledipasvir/sofosbuvir fixed dose combination tablet.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on August 7, 2014.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Linda C. Onaga, MPH Senior Regulatory Project Manager, at (301) 796-0759 or (301) 796-1500.

Sincerely,

*{See appended electronic signature page}*

Kimberly Struble, PharmD  
Cross Discipline Team Lead  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure:  
Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date and Time:** August 7, 2014 1:30 PM – 3:00 PM EST  
**Meeting Location:** Teleconference

**Application Number:** NDA 205834  
**Product Name:** ledipasvir/sofosbuvir fixed dose combination tablet  
**Applicant Name:** Gilead Sciences, Inc.

**Meeting Chair:** Kim Struble, PharmD  
**Meeting Recorder:** Linda C. Onaga, MPH

**FDA ATTENDEES**

1. John Farley, MD, Deputy Director, Office of Antimicrobial Products (OAP)
2. David Roeder, MS, Associate Director of Regulatory Affairs, OAP
3. Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
4. Jeffrey Murray, MD, MPH, Deputy Director, DAVP
5. Kim Struble, Pharm D, Cross-Discipline Team Lead, DAVP
6. Sarah Connelly, MD, Clinical Reviewer, DAVP
7. Jenny Zheng, PhD, Clinical Pharmacology Reviewer, OCP, DCPIV
8. Shirley Seo, Clinical Pharmacology Team Lead, OCP, DCPIV
9. Stacey Min, Pharm D, Acting Associate Director of Labeling, DAVP
10. Chris Ellis, PhD, Pharmacology Toxicology Reviewer, DAVP
11. Jules O'Rear, PhD, Virology Team Lead, DAVP
12. Lisa Naeger, PhD, Virology Reviewer, DAVP
13. Eric Donaldson, PhD, Virology Reviewer, DAVP
14. Karen Qi, PhD, Statistician, OB, DBIV
15. Fraser Smith, PhD, Statistician, OB, DBIV
16. Karen Winestock, Chief, Project Management Staff, DAVP
17. Linda Onaga, MPH, Senior Regulatory Project Manager
18. Christian Yoder, BSN, MPH, Regulatory Project Manager
19. Danyal Chaudhry, MS, OSE Project Manager
20. Jamie Wilkins-Parker, PharmD, DRISK Team Lead, OSE
21. Monica Calderon, PharmD, DMEPA Reviewer, OSE
22. Jeffry Florian, PhD, Pharmacometrics Team Lead, OCP, DPM

**EASTERN RESEARCH GROUP ATTENDEES**

Christopher Sees, Independent Assessor

## **APPLICANT ATTENDEES**

1. Michele Anderson, Director, Regulatory Affairs
2. Roy Bannister, PhD, DABT, Senior Director, Drug Safety Evaluation
3. Diana Brainard, MD, Senior Director, Liver Disease Therapeutics
4. Jennifer Huber, Senior Manager, Regulatory Affairs
5. Anita Mathias, PhD, Director, Clinical Pharmacology
6. Hongmei Mo, MD, Director, Clinical Virology
7. Reza Oliyai, PhD, Vice President, Formulations and Process Development
8. Phil Pang, MD, PhD, Director, Liver Disease Therapeutics and Project Leader
9. Xiaoping Qi, MS, Manager, Regulatory Affairs Labeling
10. Mani Subramanian, MD, Vice President, Liver Disease Therapeutics

### **1.0 BACKGROUND**

NDA 205834 was submitted on February 10, 2014 for ledipasvir/sofosbuvir fixed dosed combination tablet.

Proposed indication(s): treatment of genotype 1 chronic hepatic C virus infection

PDUFA goal date: October 10, 2014

FDA issued a Background Package in preparation for this meeting on July 24, 2014.

### **2.0 DISCUSSION**

#### **1. Introductory Comments**

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and cross-discipline team leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

The Division did not review the information submitted on August 7, 2014, therefore at this time we cannot provide labeling comments at this meeting. The Division is open to listening to the data submitted. We will aim to follow up with you after this meeting.

#### **2. Postmarketing Requirements/Postmarketing Commitments**

- Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response of ledipasvir/sofosbuvir in pediatric subjects 3 through 17 years of age with chronic hepatitis C.
- Collect long-term safety data for subjects enrolled in the pediatric ledipasvir/sofosbuvir safety, pharmacokinetic and efficacy study. Data collected should include at least 3 years of follow-up in order to characterize the long-term safety of ledipasvir/sofosbuvir including growth assessment, sexual maturation and characterization of ledipasvir/sofosbuvir resistance associated substitutions in viral isolates from subjects failing therapy.
- GS-US-337-0115 to provide safety data in HCV/HIV-1 subjects receiving concomitant tenofovir-containing regimens.
- GS-US-337-0123 to provide safety data in subjects with decompensated cirrhosis and/or in subjects receiving concomitant immunosuppressive agents (e.g., cyclosporine).
- Submit the final reports for the rat and mouse LDV carcinogenicity studies.
- The phenotypic assessment of NS5B\_A112T, NS5B\_E237G, and NS5B\_S473T in the HCV GT1a replicon.
- The longitudinal data on persistence of NS5A resistance substitutions from subjects who did not achieve SVR12 in the Phase 2 and 3 LDV/SOF studies in Sequence Registry Study GS-US-248-0122 and from subjects who did not achieve SVR12 in Phase 2 studies of LDV with other DAAs.

**Discussion:**

The Division provided Gilead with a list of post-marketing requirements for this NDA. A more formalized format with submission dates will be sent to Gilead following this meeting.

Gilead provided additional information on the longitudinal data on the persistence of NS5A resistance substitutions from subjects who did not reach SVR12 in Phase 2 and 3 clinical trials. Currently, the longitudinal legacy data is available for approximately 50 patients over a two year period. However, obtaining data on LDV/SOF failures is more challenging since there is only a small pool of subjects for that analysis. Of the 53 subjects who failed, 41 were retreated and achieved SVR12. The remaining 12 declined to participate in the registry. Five subjects did enter the registry; however, three dropped out and only two remain.

The Division will take this information into consideration.

3. Major Labeling Issues

Please refer to your August 2, 2014, email containing the annotated label in response to the Division's comments dated July 28, 2014. Based on your responses we are modifying the labeling discussion. In general we agree with your proposed changes with the following exceptions to be discussed on August 7, 2014.

- Section 2.1 Recommended Dose in Adults
  - The text should read “The recommended dose of [TRADENAME]...” The term dose is a single administration of a drug, whereas, the term dosage is a dosing regimen (one or more doses).
- Section 5.1 P-gp Inducers (b) (4)
  - We recommend “e.g” is retained in the statement: P-gp inducers (e.g., rifampin or St. John’s wort)...
  - This comment also applies to section 7
- Section 5.2 (b) (4)
  - (b) (4)
  - (b) (4)
- Section 7: Drug Interactions
  - We agree with your clinical comment for H2-receptor antagonists
  - We are deferring labeling recommendations for use with tenofovir (see comments above).
- Section 12.3 (b) (4)
  - (b) (4)
  - We agree with the proposed inclusion of (b) (4) data.
- Section 12.4: Microbiology
  - Minor edits were made to this section and are forthcoming. Additionally, statements regarding treatment-emergent NS5B substitutions were also added.

- Section 14: Clinical Studies

- We agree with including the SVR12 rates from the 8 and 12 week treatment arms in subjects with baseline HCV RNA < 6 million IU/mL.
- Please propose text to discuss the concordance between SVR12 and SVR24 data from ION-2.

**Discussion:**

The Division provided Gilead with updated labeling to facilitate the late cycle meeting. Upon review of the Division's recommendations and revisions, Gilead agreed to the changes proposed. Gilead will provide the Division with updated labeling reflecting the agreement after the meeting.

Prior to the meeting, Gilead sent additional safety information on tenofovir exposures observed with LDV/OF plus Atripla co-administration with median 10.5 week duration although the Division requested 12 weeks duration. The Division did not have enough time to have internal discussions on the information provided, but will respond to Gilead after the LCM. Gilead gave a brief high level summary of the information provided and will wait for the Division's response.

The Division suggest Gilead wait to submit the label since additional labeling comments regarding tenofovir exposures with LDV/SOF are forthcoming.

4. Review Plans

- Finalize LDV/SOF labeling
- Await facility inspection reports

**Discussion:**

Gilead inquired about the Division's timeline to take action, and if an early action is possible because the inspections were completed and labeling is near final. A number of factors will determine if the Division can take an earlier action for this application, including completion of supervisory reviews, additional labeling negotiations, and facility inspection reports. According to Gilead, inspections went well with only two minor observations.

The Division is waiting for the District office to provide headquarters with their final assessment. Until then, the Division is unable to commit to an early action date.

5. Wrap-up and Action Items

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/  
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DEBRA B BIRNKRANT  
09/05/2014





NDA 205834

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

Gilead Sciences, Inc.  
Attention: Michele Anderson  
Associate Director, Regulatory Affairs  
333 Lakeside Drive  
Foster City, CA 94404

Dear Ms. Anderson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ledipasvir/sofosbuvir fixed dose combination tablet.

We also refer to the Late-Cycle Meeting (LCM) scheduled for August 7, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Linda C. Onaga, MPH Senior Regulatory Project Manager, at (301) 796-0759 or (301) 796-1500

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:  
Late-Cycle Meeting Background Package

## **LATE-CYCLE MEETING BACKGROUND PACKAGE**

**Meeting Date and Time:** August 7, 2014 1:30 PM – 3:00 PM EST  
**Meeting Location:** 10903 New Hampshire Ave  
Bldg 22 Room 1311  
Silver Spring, MD 20993

**Application Number:** NDA 205834  
**Product Name:** ledipasvir/sofosbuvir fixed dose combination tablet  
**Indication:** treatment of genotype 1 chronic hepatitis C virus infection  
**Sponsor/Applicant Name:** Gilead Sciences, Inc.

### **INTRODUCTION**

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and cross-discipline team leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

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### **Discipline Review Letters**

No Discipline Review letters have been issued to date.

### **Substantive Review Issues**

At this time we do not have any substantive review issues. However, if we learn of any issues from the outstanding CMC inspections, then the agenda will be modified accordingly.

### **ADVISORY COMMITTEE MEETING**

An Advisory Committee meeting is not planned.

### **REMS OR OTHER RISK MANAGEMENT ACTIONS**

No issues related to risk management have been identified to date.

## LCM AGENDA

### 1. Introductory Comments – Linda C. Onaga, MPH/Kimberly Struble, PharmD

Welcome, Introductions, Objectives of the meeting

### 2. Postmarketing Requirements/Postmarketing Commitments – 15 minutes

- GS-US-337-0115 to provide safety data in HCV/HIV-1 subjects receiving concomitant tenofovir-containing regimens.
- GS-US-337-0123 to provide safety data in subjects with decompensated cirrhosis and/or in subjects receiving concomitant immunosuppressive agents (e.g., cyclosporine).
- The final reports for the rat and mouse carcinogenicity studies.
- The longitudinal data on persistence of NS5A resistance substitutions from subjects who did not achieve SVR12 in the Phase 2 and 3 LDV/SOF studies in Sequence Registry Study GS-US-248-0122 and from subjects who did not achieve SVR12 in Phase 2 studies of LDV with other DAAs.
- The phenotypic assessment of NS5B\_A112T, NS5B\_E237G, and NS5B\_S473T in the HCV GT1a replicon.

### 3. Major labeling issues – 60 minutes

Please note the labeling discussion may be modified depending on subsequent revisions to the labeling. We will discuss with you any revisions to the agenda prior to August 7, 2014.

- Section 5 Warnings and Precautions
  - Changes in terminology “(b) (4)” to the use is not recommended”
- Section 6: Adverse Reactions – Laboratory Abnormalities subsection
  - Removal of safety findings from (b) (4)
  - Addition of bilirubin elevations
- Section 7: Drug Interactions
  - Deletion of (b) (4)” to describe P-gp inducers

- Recommendations for H<sub>2</sub>-receptor antagonists and proton pump inhibitors
  - Use with TDF containing regimens
  - Other edits to antimycobacterials and simeprevir
  - Section 8.1 Pregnancy
    - Edits to Animal Data subsection
  - Section 8.3 Nursing Mothers
  - Section 12 Clinical Pharmacology
    - Table 5: Inclusion of data from (b) (4) trial
  - Section 12.4 Microbiology
    - Edits to *In Clinical Trials* and Effect of Baseline HCV Polymorphisms on Treatment Response subsections
  - Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
    - Revisions to the two year carcinogenicity study results for sofosbuvir
    - Impairment of Fertility – updated numbers based on Day 14 exposure data from study TX-256-2003
  - Section 13.2 Animal Toxicology and/or Pharmacology
    - Removal of (b) (4) and edits to sofosbuvir subsection regarding exposures and doses
4. Review Plans – 10 minutes
- Finalize LDV/SOF labeling
  - Await facility inspection reports
5. Wrap-up and Action Items – 5 minutes

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/s/  
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DEBRA B BIRNKRANT  
07/24/2014