

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205834Orig1s007, s008, s009

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 205834 – Harvoni, supplements 7, 8 and 9

Product Name: _____

PMC Description: Collect, analyze and submit data on subjects with cirrhosis including decompensated cirrhosis who achieve sustained virologic response following treatment with a sofosbuvir-based regimen to evaluate durability of virologic response and to characterize clinical outcomes such as progression or regression of liver disease, liver-related mortality, occurrence of hepatocellular carcinoma, or liver failure requiring liver transplantation. Data collected should include 5 years of follow-up.

PMC Schedule Milestones:	Final Protocol Submission:	<u>08/2015</u>
	Study/Trial Completion:	<u>10/2021</u>
	Final Report Submission:	<u>10/2022</u>
	Other:	<u>n/a</u>

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

At present, there are very limited available treatment options for chronic hepatitis C (CHC) patients with decompensated cirrhosis or for those who are liver transplant recipients. Without a liver transplantation, the one-year mortality is estimated to range from at least 30% to 50% in such patients. Harvoni is approved for the treatment of CHC in patients without cirrhosis or with compensated cirrhosis genotypes 1, 4, 5 or 6. Supplements 7-9 NDA 205834 support extending the current existing indication to patients with decompensated cirrhosis genotype 1 and to patients with genotype 1 or 4 HCV infection who are liver transplant recipients. The approval relies on efficacy measured as sustained virologic response (SVR) at 12 weeks posttreatment, SVR12 being an accepted benchmark of hepatitis C virologic cure. We are requesting commitment to submit in the postmarketing period data evaluating the durability of virologic response in the population with cirrhosis including decompensated cirrhosis. Additionally, we are requesting commitment to submit in the postmarketing period, data evaluating the longer term impact of SVR on important clinical outcomes including progression or regression of liver disease, and liver-related mortality. These data will provide information about the impact of treatment on clinical endpoints in patients with cirrhosis including decompensated cirrhosis.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The pertinent clinical issues are stated in the response to #1. The goal of the trial will be 1) obtain follow-up data in patients who have attained SVR12 in order to assess durability of response over 5 years, and 2) to evaluate the impact of SVR12 on important clinical endpoints such as progression or regression of liver disease, liver-related mortality, occurrence of hepatocellular carcinoma, or liver failure requiring liver transplantation.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

CHRISTIAN P YODER
02/12/2016

Division of Antiviral Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 205834/ S-7, S-8, S-9

Name of Drug: Harvoni (ledipasvir and sofosbuvir) tablets

Applicant: Gilead Sciences, Inc.

Labeling Reviewed

Submission Date: February 7, 2016

Receipt Date: February 8, 2016

Background and Summary Description:

Gilead submitted three efficacy supplements that proposed the following changes based on the results from the SOLAR-1 and SOLAR-2 clinical trials:

NDA 205834/S-7

- To expand the patient population to include subjects with genotype 1, chronic hepatitis C virus infection who are liver transplant recipients

NDA 205834/S-8

- To expand the patient population to include subjects with genotype 4, chronic hepatitis C virus infection who are liver transplant recipients without cirrhosis, or with compensated cirrhosis

NDA 205834/S-9

- To expand the patient population to include subjects with decompensated cirrhosis who have genotype 1, chronic hepatitis C virus infection.

Review

1. In the HIGHLIGHTS OF PRESCRIBING INFORMATION the following changes have been proposed:

RECENT MAJOR CHANGES has been updated as follows:

-----RECENT MAJOR CHANGES -----	
Indications and Usage (1)	11/2015
Dosage and Administration (2.1)	<u>02/2016</u>

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

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/s/

CHRISTIAN P YODER
02/12/2016

KAREN D WINESTOCK
02/12/2016

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 205834, Supplements 7, 8, & 9

Application Type: Efficacy Supplement

Name of Drug/Dosage Form: Harvoni (ledipasvir and sofosbuvir) oral tablets 90/400 mg

Applicant: Gilead Sciences, Inc.

Receipt Date: August 26, 2015

Goal Date: February 26, 2016

1. Regulatory History and Applicant's Main Proposals

Gilead Sciences, Inc. has submitted three efficacy supplements (7, 8, & 9) seeking to expand the potential benefit of Harvoni (ledipasvir and sofosbuvir). Two Phase 2 studies (SOLAR-1) and (SOLAR-2) included in the application support the safety and efficacy of Harvoni plus ribavirin for 12 weeks in patients with HCV infection who are post-transplantation with compensated liver disease (genotype 1 and genotype 4 HCV) as well as patients with decompensated liver disease (genotype 1 HCV), regardless of transplantation status. The SOLAR-1 study also fully addresses Postmarketing Requirement 2780-7 which requires the final report and datasets 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).

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by **DATE** (choose a date within three weeks of the letter). The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- NO** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment: *The horizontal line separating the TOC from the FPI is missing.*

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required

Selected Requirements of Prescribing Information

• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Selected Requirements of Prescribing Information

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- YES** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- YES** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- YES** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES

Selected Requirements of Prescribing Information

21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- NO** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment: The subsection heading of TOC Section 14.4 does not match the subsection heading in the FPI - "...Decompensated Liver Disease." vs. "...Decompensated Cirrhosis."
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

YES

Selected Requirements of Prescribing Information

34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

YES 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

YES 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

CHRISTIAN P YODER
02/11/2016

KAREN D WINESTOCK
02/12/2016

This review was completed in October 2015, but the document was not placed in DARRTs.

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: February 4, 2016

To: Christian Yoder, Regulatory Project Manager
Division of Antiviral Products

From: Jessica Fox, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion

Subject: NDA 205834 Supplements 7, 8, and 9
HARVONI (ledipasvir and sofosbuvir) tablets, for oral use

As requested in the Division of Antiviral Products' (DAVP) consult dated September 4, 2015, the Office of Prescription Drug Promotion (OPDP) has reviewed the HARVONI prescribing information and patient labeling.

OPDP reviewed the proposed substantially complete version of the prescribing information sent via email on January 20, 2016, and has provided comments in the attached labeling, specifically on page 39 of the document.

The Division of Medical Policy Programs and OPDP provided a single, consolidated review of the patient labeling on February 3, 2016.

Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact Jessica Fox at (301) 796-5329 or Jessica.Fox@fda.hhs.gov.

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/s/

JESSICA M FOX
02/04/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: February 2, 2016

To: Debra Birnkrant, MD
Director
Division of Antiviral Products (DAVP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Morgan Walker, PharmD, MBA
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Jessica Fox, PharmD, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): HARVONI (ledipasvir and sofosbuvir)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 205834

Supplement Number: S-007, S-008, S-009

Applicant: Gilead Sciences, Inc.

1 INTRODUCTION

On September 2, 2015, Gilead Sciences, Inc. submitted for the Agency's review three efficacy supplements (S-007, S-008, S-009) to their New Drug Application (NDA) 205834 for HARVONI (ledipasvir and sofosbuvir) tablets, for oral use. The efficacy supplements provide for the following proposed changes to the Dosage and Administration section of the Prescribing Information:

- S-007: Include liver transplant recipients with genotype 1 chronic hepatitis C virus infection.
- S-008: Include liver transplant recipients with genotype 4 chronic hepatitis C virus infection.
- S-009: Include patients with decompensated cirrhosis with genotype 1 chronic hepatitis C virus infection.

HARVONI (ledipasvir and sofosbuvir) was originally approved on October 10, 2014 and is currently indicated for the treatment of patients with chronic hepatitis C virus (HCV) genotype 1, 4, 5 or 6 infection.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antiviral Products (DAVP) on September 8, 2015, for DMPP and OPDP to review the Applicant's proposed Package Insert (PPI) for HARVONI (ledipasvir and sofosbuvir) tablets.

2 MATERIAL REVIEWED

- Draft HARVONI (ledipasvir and sofosbuvir) tablets PPI received on September 2, 2015, and received by DMPP and OPDP on January 20, 2016.
- Draft HARVONI (ledipasvir and sofosbuvir) tablets Prescribing Information (PI) received on September 2, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 20, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible

- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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

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/s/

MORGAN A WALKER
02/02/2016

JESSICA M FOX
02/02/2016

BARBARA A FULLER
02/02/2016

LASHAWN M GRIFFITHS
02/03/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Drug Utilization Review**

Date: 12/18/2015

Reviewer(s): Nabila Sadiq, PharmD.
Drug Utilization Analyst
Division of Epidemiology II

Team Leader Mohamed A. Mohamoud Pharm.D., MPH, BCPS
Drug Utilization Team Leader
Division of Epidemiology II

Deputy Director Grace Chai, Pharm.D.
For Drug Utilization: Division of Epidemiology II

Drug Name(s): Sovaldi[®], Harvoni[®] & Daklinza[®]

Application Type/Number: 204671, 205834, 206843

Applicant/sponsor: Gilead, Bristol-Myers Squibb

OSE RCM #: 2015-2449, 2015-2451

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

1 INTRODUCTION

1.1 BACKGROUND

The purpose of this review is to provide the Division of Antiviral Products (DAVP) with drug use data for Sovaldi[®] (Sofosbuvir), Harvoni[®] (Ledipasvir/Sofosbuvir) and Daklinza[®] (Daclatasvir). These data will be used to support an ongoing post marketing safety review related to the aforementioned drugs.

In an effort to support DAVP in this post marketing safety review, the Division of Epidemiology II (DEPI II) is providing drug use data for Sovaldi[®], Harvoni[®] and Daklinza[®]. The drug use data provided in this review will span the time period from the date of approval of each product through September 2015 (*Table 1*).

1.2 PRODUCT INFORMATION

Sovaldi[®] is a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor indicated for the treatment of chronic hepatitis C infection (CHC) in adult patients with genotype 1,2,3,4, as a component of a combination antiviral treatment regimen with peg-interferon alfa or ribavirin. Sovaldi[®] is available as 400mg tablets for oral administration¹.

Harvoni[®] is a fixed-dose combination of ledipasvir, a hepatitis C virus (HCV) NS5A inhibitor, and sofosbuvir, an HCV nucleotide analog NS5B polymerase inhibitor, indicated for the treatment of chronic hepatitis C virus (HCV) genotype 1, 4, 5 or 6 infections. Harvoni[®] is available as 90 mg of ledipasvir and 400 mg of sofosbuvir tablet for oral administration².

Daklinza[®] is hepatitis C virus (HCV) NS5A inhibitor, indicated for the treatment of genotype 3 chronic HCV infections in patients with compensated liver disease in combination with Sovaldi. Daklinza[®] is available as 30mg and 60mg tablets for oral administration³.

¹ U.S. Food and Drug Administration: Drugs@FDA. Sovaldi Label Information. Accessed November 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/204671s002lbl.pdf

² U.S. Food and Drug Administration: Drugs@FDA. Harvoni Label Information. Accessed November 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205834s006lbl.pdf

³ U.S. Food and Drug Administration: Drugs@FDA. Harvoni Label Information. Accessed November 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206843Orig1s000lbl.pdf

TABLE I^{1,2,3}

Product	Date of approval	Strength	Manufacturer
Sovaldi (Sofosbuvir)	December, 2013	400mg tablets (prescribed in combination with daclatasvir or, ribavirin, or peginterferon alfa/ribavirin)	Gilead
Harvoni (Ledipasvir/Sofosbuvir)	October, 2014	90mg/400mg (Single dose regimen)	Gilead
Daklinza (Daclatasvir)	July, 2015	30 & 60 mg tablets (prescribed in combination with sofosbuvir 400 mg)	Bristol-Myers Squibb

1.3 METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct this analysis. (See Appendix for full database description)⁴.

1.4 DETERMINING SETTING OF CARE

The IMS Health, IMS National Sales PerspectivesTM (see Appendix for full database description) was used to determine the various retail and non-retail channels for distribution for Sovaldi[®], Harvoni[®] and Daklinza[®].

Sales data from date of approval through September 2015 indicated that approximately (b) (4) % of Sovaldi[®] bottles were distributed to mail-order/specialty pharmacies, (b) (4) % to outpatient retail and (b) (4) % to non-retail pharmacy settings of care.

Sales data from date of approval through September 2015 indicated that approximately (b) (4) % of Harvoni[®] bottles were distributed to mail-order/specialty pharmacies, (b) (4) % to outpatient retail, and (b) (4) % to non-retail pharmacy settings.

Sales data from date of approval through September 2015 indicated that approximately (b) (4) % of Daklinza[®] bottles were distributed to mail-order/specialty pharmacies, (b) (4) % to outpatient retail, and (b) (4) % to non-retail pharmacy settings.

As a result of these sales distribution patterns, drug utilization data from mail-order/specialty pharmacy and outpatient retail settings were examined in this review.

⁴ IMS Health, IMS National Sales PerspectivesTM, Date of approval, September 2015. Extracted November 2015. Source file: 2015-2449_2015-2451 NSP- Sovaldi-Harvoni- Daklinza Date of approval- Sep 2015 11.20.2015.xlsx

Non-retail pharmacy data including hospitals and clinics were not included in this analysis.

1.5 DATA SOURCES USED

(b) (4)
database was used to obtain the nationally estimated number of patients who received a dispensed prescriptions for Sovaldi[®], Harvoni[®] and Daklinza[®] from date of approval of each product through September 2015, from U.S. mail order/specialty and outpatient retail pharmacies, stratified by patient age (0-16, 17-49, 50-64, 65+ years).

2 RESULTS

2.1 PATIENT DATA FOR SOVALDI[®], HARVONI[®] & DAKLINZA[®]

Table 2 shows the nationally estimated number of patients stratified by age (0-16, 17-49, 50-64, 65+ years) who received a dispensed prescription for Sovaldi[®] and/or Harvoni[®] and/or Daklinza[®] from U.S mail order/specialty and outpatient retail pharmacies, from date of approval through September 2015.

Approximately (b) (4) patients received a dispensed prescription for Sovaldi[®] from date of approval through September 2015. The majority of Sovaldi[®] use was among patients between the ages of 50-64 years of age accounting for 62% ((b) (4) patients), followed by patients 17-49 years and 65+ years with 19% ((b) (4) patients), respectively.

Approximately (b) (4) patients received a dispensed prescription of Harvoni[®] from date of approval through September 2015. The majority of use was again among patients between the ages of 50-64 years of age accounting 65% ((b) (4) patients), followed by patients 65+ years and 17-49 years with 20% ((b) (4) patients) and 15 % ((b) (4) patients) of total patients, respectively.

Approximately (b) (4) patients received a dispensed prescription for Daklinza[®] from date of approval through September 2015. The majority of the use was among patients between the ages of 50-64 years of age accounting for 61% ((b) (4) patients), followed by patients 17-49 years and 65+ years with 25% ((b) (4) patients) and 14 % ((b) (4) patients) of total patients, respectively.

The use of Sovaldi[®], Harvoni[®] and Daklinza[®] among patients 0-16 years was less than 1% with only 160, 34 and 6 unique patients, respectively.

Table 2

Nationally estimated number of patients who received a dispensed prescription for Harvoni and/or Sovaldi and/or Daklinza* from U.S. mail order/outpatient retail pharmacies, stratified by patient age, from date of drug approval** through September 2015, cumulative				
	Patient (N)	Share (%)		
Sovaldi	(b) (4)	(b) (4)		
0-16 Years				
17-49 Years				
50-64 Years				
65+ Years				
Unspecified age				
Harvoni		(b) (4)	(b) (4)	
0-16 Years				
17-49 Years				
50-64 Years				
65+ Years				
Unspecified age				
Daklinza			(b) (4)	(b) (4)
0-16 Years				
17-49 Years				
50-64 Years				
65+ Years				
Unspecified Age				

*subtotals may not sum exactly, due to patients aging during the study period (“the cohort effect”), and may be counted more than once in the individual age categories. For this reason, summing across patient age bands is not advisable and will result in overestimates of patient counts

**Sovaldi: December 2013, Harvoni: October 2014, Daklinza: July 2015

Source: (b) (4)™ Extracted November 2015 Source File (b) (4) 2015-2449- 2015-2551 Sovaldi, Harvoni, Daklinza age group report 11 18 15 xls

3 LIMITATIONS

Our analysis shows that despite being approved after Sovaldi, Harvoni had the largest number of patients among the three examined oral Hepatitis C drugs across the examined time from approval of each drug through September 2015. The relatively low use of Daklinza® is most likely due to its recent approval for marketing (i.e. July 2015). Of note, this review does not provide any information on the concurrent use of Sovaldi with peg-interferon alfa, ribavirin or daclatasvir. Less than 0.5% of patients were captured in the database to be younger than 17 years of age. However, no patient chart validation is available, possible data errors such as use in young patients cannot be verified.

Our results should be interpreted in the context of the known limitations of the databases used. Based on IMS National Sales Perspectives™ sales data for the examined time period, approximately (b) (4)% of Sovaldi®, (b) (4)% of Harvoni® and (b) (4)% of Daklinza® bottles were distributed to the mail-order/specialty pharmacy setting, followed by approximately (b) (4)% to the outpatient retail pharmacy setting for all three products. As a result of the sales distribution patterns, we focused our analysis only on the mail-order/specialty and

outpatient retail pharmacy settings. As such, these results may not apply to other settings of care in which these products are used such as clinics, hospitals, as well as other health care settings.

4 CONCLUSIONS

The drug utilization data provided in this review is to assist DAVP with their on-going post-market safety assessment of Sovaldi[®], Harvoni[®] and Daklinza[®]. Among the three drugs used to treat hepatitis C examined in this review, Harvoni[®] showed the largest number of patients during the examined time periods. Although these data are useful in providing national estimates of patients dispensed a prescription for Sovaldi[®], and/or Harvoni[®] and/or Daklinza[®] from U.S. outpatient retail and mail-order/specialty pharmacy settings, our results should not be overstated and do not apply to other settings of care where these products are used, such as hospitals and clinics.

APPENDICES

APPENDIX 1: DATABASE DESCRIPTION

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

(b) (4) **TM**

The (b) (4) is a syndicated view of U.S. retail and mail order pharmacy patient prescription activity, updated on a monthly basis at a projected national level. (b) (4) Patient monthly is based on the (b) (4) longitudinal patient data source, which captures adjudicated prescription claims across the United States across all payment types, including commercial plans, Medicare Part D, cash, assistance programs, and Medicaid. The database contains approximately 10 billion prescriptions claims linked to over 220 million unique prescription patients with an average of 4.2 years of prescription drug history, of which approximately 140 million patients are linked to a diagnosis.

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/s/

NABILA SADIQ
02/02/2016

MOHAMED A MOHAMOUD
02/02/2016

GRACE CHAI
02/02/2016

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: December 29, 2015

TO: Christian Yoder, Regulatory Health Project Manager
Charu Mullick, M.D., Medical Officer
Division of Antiviral Products

FROM: Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Susan Thompson, M.D./ for
Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 205834/S7-9

APPLICANT: Gileads Sciences, Inc.

DRUG: Harvoni™ (ledipasvir/sofosbuvir)

NME: No

THERAPEUTIC CLASSIFICATION: Priority review

INDICATION: Treatment of chronic genotype 1& 4 HCV-infection in adults, in patients with chronic hepatitis C with advanced liver disease or are post-liver transplant

CONSULTATION REQUEST DATE: September 23, 2015

DIVISION ACTION GOAL DATE: February 26, 2016

PDUFA DATE: February 26, 2016

INSPECTION SUMMARY DUE DATE: January 29, 2016

I. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Four clinical investigator sites were inspected in support of this application. The inspection of the four clinical investigators listed below revealed minor regulatory violations (Dr. Brown). The pending classification for Dr. Brown is Voluntary Action Indicated (VAI). The Pending classification for Drs. Everson, Yoshida, and Casteillo sites are No Action Indicated (NAI). For the pending classifications, a summary addendum will be generated if conclusions change upon receipt and review of the EIRs. Overall, the data submitted from these four sites are considered acceptable and may be used in support of the pending application.

II. BACKGROUND:

GS-5885 is a novel HCV NS5A inhibitor that has demonstrated a potent anti-HCV activity against genotype (1a and 1b) HCV infection. More than 1000 HCV infected subjects have been dosed with GS-5885 in ongoing Phase 2 clinical studies, and over 700 subjects have been dosed with GS-5885 for over 12 weeks. The applicant is seeking the following indication: the treatment of chronic hepatitis C (CHC) genotype 1 and 4 infection, in combination with and without ribavirin, in adults with advanced liver disease or are post-liver transplant patients.

The Applicant-sponsored two studies: Study Protocols GS-US-337-0123 for treatment of genotype 1 and 4 HCV-infected subjects (domestic), and GS-US-337-0124 for treatment of genotype 1 and 4 HCV subjects (foreign) with advanced liver disease or are post-liver transplant were submitted in support of the application.

Protocols GS-US-337-0123 & GS-US-337-0124

These protocols are essentially the same; therefore, a single description of the key design features is presented below; Protocol GS-US-337-0123 (domestic) and GS-US -337-0124 (foreign).

Protocol GS-US-337-0123 is 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 Treatment”.

The objectives of this study were: 1) to explore the antiviral efficacy of combination therapy with SOF/LDV FDC=RBV for 12 or 24 weeks in subjects with advanced liver disease (either pre-liver transplant or not currently wait-listed) and post-liver transplant HCV subjects with cirrhosis as measured by SVR 12 weeks after discontinuation of therapy (SVR12 defined as HCV RNA < Lower Limit of Quantification (LLOQ) 12 weeks post-treatment, and 2) to evaluate the safety and tolerability of SOF/LDV FDC + RBV administered for 12 or 24 weeks in each patient population.

The secondary objective of this study was: 1) to determine the proportion of subjects who attain SVR at 2, 4, 8, and 24 weeks after discontinuation of therapy (SVR4, SVR8, and SVR 24).

This protocol was a multicenter, open-label study in genotype 1 and 4 HCV-infected adult male and female subjects. The target was to enroll 400 subjects in the study. Subjects were randomized to receive 12 or 24 weeks of dosing with SOF/LDV FDC given once daily) + ribavirin (given as a divided dose twice daily). Approximately 100 subjects were enrolled in Cohort A and 300 in Cohort B: each group enrolled 50 subjects (25 randomized to 12 weeks of study drug and 25 subjects randomized to 24 weeks of study drug treatment) with the exception of Cohort B which enrolled 100 subjects; 50 subjects randomized to 12 weeks of drug treatment and 50 subjects randomized to 24 weeks to treatment.

Cohort A - Advanced Liver Disease

- Group 1 : Subjects with cirrhosis and moderate hepatic impairment (Class B)
- Group 2 : Subjects with cirrhosis and severe hepatic impairment (Class C)

Cohort B - Post-Liver Transplant

- Group 3: Subjects without cirrhosis (fibrosis stage F0-F3 and with no evidence of hepatic decompensation)
- Group 4: Subjects with cirrhosis and mild hepatic impairment (Class A).

The Division of Antiviral Products (DAVP) requested inspections of the following clinical investigator sites due to high subject enrollment, and significant efficacy results pertinent to decision-making. Study GS-US-337-0124 was not conducted under an IND and was conducted at sites outside the United States. Site selection was a team effort with statistical input.

III. RESULTS (by protocol/site):

Name of CI, Location, and Site #	Protocol and # of Subjects Randomized	Inspection Dates	Final Classification
Robert Brown, M.D Columbia University 859 Presbyterian Hospital New York, NY 10032 Site #0522	Protocol GS-US-337-0123SOLAR -1 Number of subjects: 18	10/20-23/2015	Pending (preliminary classification VAI)
Gregory Everson, M.D. University of Colorado 1240E 17th Avenue Aurora, CO 80045 Site #1249	Protocol GS-US-337-0123SOLAR-1 Number of subjects: 19	12/2-9/2015	Pending (preliminary classification NAI)
Eric Yoshida, M.D. 5153-2775 Laurel St. V5Z1m9 Vancouver, BC Canada Site #0452	Protocol GS-US-337-0124SOLAR-2 Number of subjects: 12	12/7-10/2015	Pending (preliminary classification NAI)

Name of CI, Location, and Site #	Protocol and # of Subjects Randomized	Inspection Dates	Final Classification
Martin P. Casteillo, M.D. Buleva Sur s/n Servixcio Neurologia 46026 Valencia Spain Site # 1222	Protocol GS-US-337-0124SOLAR-2 Number of subjects 20	12/12-18/2015	Pending (preliminary classification NAI)

Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations. Data are unreliable.

Pending = Preliminary classification based on e-mail communication from the field; the Establishment Inspectional Report (EIR) has not been received from the field and complete review of EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

1. Robert S. Brown, M.D. New York, NY 10032

At this site, a total of 22 subjects were screened, 2 subjects were reported as screen failures, 18 subjects were randomized into the study, 17 subjects completed the study, and one subject was discontinued but completed follow-up visits.

The medical records/source data for 11 subjects were reviewed in depth. In addition, the informed consent process, adverse events, and primary efficacy endpoints were verified for all 18 subjects. The review included drug accountability records, inclusion/exclusion criteria, vital signs, IRB records, sponsor correspondence, and adverse events. Source documents for all subjects reviewed were compared to case report forms and data listings including primary efficacy endpoints and adverse events listings.

At the conclusion of the inspection, a 3-item Form FDA 483 was issued to Dr. Brown. Our ORA investigator found protocol violations and inadequate record keeping.

Protocol violations:

Three subjects 75121, 75323, and 75229 experienced adverse events which were not recorded in their respective e-CRFs.

- Subject 57121 experienced anemia which was recorded on the subject's adverse event log, but was not recorded in the subject's e-CRF
- Subject 75323 amputation right toe, cellulitis of the right lower extremity and wound infection were included in the adverse event log for the subject but were not documented in the e-CRFs as individual adverse events.

- Subject 75329 experienced dehydration which was recorded on the subject's adverse event log, but was not recorded in the subject's e-CRF.
- Subject 75707 received the prohibited medication ranitidine HCL 300mg oral capsule which was allowed by the protocol at a maximum dose of 150 mg/day. This subject was given 300 mg/day contrary to the protocol.
- Subject 75211 took Nexium (a proton pump inhibitor) during the study. A similar observation was noted for Subject 75229. The use of proton pump inhibitors were disallowed by the protocol, but were acceptable if clinically indicated.

Inadequate record keeping:

The IRB continuing review letter dated July 22, 2014 noted the approval of ICF Version 2 which required written re-consent of all enrolled subjects to reflect the safety information that was removed from the informed consent document, as well as a new rare, but serious, risk that pertained specifically to hemophiliac patient. The clinical investigator did not obtain the IRB required re-consent from at least 8 subjects. All 8 subjects remained on the study during the follow-up at the time the updated informed consent form was approved by the IRB.

The clinical investigator agreed with the observations in his written response dated November 11, 2015 in which he promised to implement corrective action plan to prevent the recurrence of the inspectional findings. In addition, he stated that the adverse events noted above were reported in the narrative of the SAE report. OSI finds his response acceptable.

With the exceptions noted above, the medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths, and no evidence of under-reporting of adverse events the exception clarified above. There were no known limitations to the inspection.

Although regulatory violations were noted, the findings are not likely to affect data integrity. The data generated by this site are considered reliable and appear acceptable in support of the pending applications.

**2. Gregory Everson, M.D.
Aurora, CO 80045**

At this site, a total of 24 subjects were screened, six subjects were reported as screen failures, 18 subjects were randomized into the study, one subject transferred to the site, and 19 subjects completed the study.

The medical records/source data for 19 subjects were reviewed including drug accountability records, vital signs, IRB records, informed consent documents, prior and current medications, and inclusion/exclusion criteria. Source documents for all subjects were compared to data listings for primary efficacy endpoints and adverse events listings.

At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Everson. However, the ORA investigator found one subject who had a medical history of Pruritus and was taking rifampin a prohibited concomitant medication at the time of screening, the week of Visit 1. The medical monitor acknowledged the medication and stated that there was no safety issue for the subject and allowed the subject to continue on the study. The medical records reviewed were verifiable based on the information available at the site. There were no known limitations to the inspection. There were no deaths and no evidence of under-reporting of adverse events at this site.

Overall, the data submitted in support of the clinical efficacy and safety from this site is considered reliable and may be used in support of the pending applications.

**3. Eric Yoshida, M.D.
British Columbia, Canada**

At this site, a total of 13 subjects were screened, one subject was reported as a screen failure, and 12 subjects were randomized into the study. Six subjects completed the study, and two subjects were withdrawn from the study due to incarceration.

The medical records/source data for 12 subjects were reviewed and compared to data listings. The review included drug accountability records, informed consent documents, inclusion/exclusion criteria, vital signs, IRB records, sponsor correspondence, and adverse events. Source documents for all subjects were compared to case report forms and data listings including for primary efficacy endpoints and adverse events listings. No deficiencies were noted.

At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Yoshida. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.

Overall the data generated by this site are considered reliable and appear acceptable in support of the pending application.

**4. Martin P. Casteillo, M.D.
46026 Valencia, Spain**

At this site, a total of 20 subjects were screened, six subjects were reported as screen failures, 14 subjects were randomized into the study, 14 subjects completed the study, and two subjects were withdrawn from the study due to incarceration.

The medical records/source data for 14 subjects were reviewed and compared to data listings. The review included drug accountability records, informed consent documents, inclusion/exclusion criteria, vital signs, IRB records, sponsor correspondence, and adverse events. Source documents for all subjects were compared to case report forms and data listings including for primary efficacy endpoints and adverse events listings. No deficiencies were noted.

At the conclusion of the inspection, no Form FDA 483 was issued to Dr.Casteillo. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.

Overall the data generated by this site are considered reliable and appear acceptable in support of the pending application.

{See appended electronic signature page}

Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
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SUSAN D THOMPSON
01/04/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Pharmacovigilance Review

Date: December 4, 2015

Reviewer: Mihaela Jason, PharmD
Division of Pharmacovigilance II

Team Leader: Kelly Cao, PharmD
Division of Pharmacovigilance II

Deputy Division Director: S. Christopher Jones PharmD, MS, MPH
Division of Pharmacovigilance II

Product Name: Harvoni (ledipasvir/sofosbuvir)

Subject: All adverse events with ledipasvir/sofosbuvir use

Application Type/Number: NDA 205834

Applicant/Sponsor: Gilead Sciences, Inc.

OSE RCM #: 2015-2318

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EXECUTIVE SUMMARY

This review evaluates the FDA Adverse Event Reporting System (FAERS) for post-marketing reports of adverse events with the use of Harvoni (ledipasvir/sofosbuvir). The Division of Antiviral Products (DAVP) consulted the Division of Pharmacovigilance II (DPV II) to assess all adverse events in light of several supplements submitted by the sponsor to expand indications to liver transplant recipients with genotype 1 and 4 hepatitis C virus (HCV) infection, as well as patients with decompensated cirrhosis with genotype 1 HCV infection.

A review of the most frequently reported PTs for all reports, deaths, and DMEs identified PTs that were labeled (e.g., headache, fatigue, nausea, insomnia, diarrhea, malaise) or liver disease related (e.g., encephalopathy, hepatic failure, ascites).

There were three cases of hypertensive crisis that support a drug-event association based on temporal association. One patient also experienced a subarachnoid hemorrhage. However, the cases were confounded by elevated BP at baseline and concomitant medications and comorbidities. A literature review did not find any published information supporting a relationship between SOF or SOF/LDV and hypertensive crisis or cerebral hemorrhage. Due to the small number of cases and the confounding factors, there is insufficient information to support a new safety signal. DPV II will continue to monitor for cases of hypertensive crisis and cerebral hemorrhage reported with SOF and SOF/LDV.

One case of pancreatitis with a temporal association to LDV/SOF was identified. However, the case was confounded by concomitant medications associated with pancreatitis. Due to only having a single case and the confounding factors, a definitive causal relationship between LDV/SOF and pancreatitis cannot be made at this time. DPV II will continue to monitor for cases of pancreatitis reported with LDV/SOF use.

The severity of the cases describing severe cutaneous adverse reactions was consistent with what was identified in the previous 6 months review.³ There were no cases of SJS or TEN reported.

Cases reporting the unlabeled events of anemia, renal failure, and hepatic decompensation and failure will be assessed in a separate DPV II review. Hepatic decompensation and failure in patients with HCV infection are not unexpected; however, given the concerns of hepatotoxicity with other direct acting antivirals, such as simeprevir and Viekira Pak, we plan to evaluate this signal further.

No new safety signals were identified in this review of FAERS post-marketing reports of LDV/SOF use. DPV II will continue to monitor for all adverse events associated with the use of LDV/SOF.

1 INTRODUCTION

1.1 BACKGROUND

This review evaluates the FDA Adverse Event Reporting System (FAERS) for post-marketing reports of adverse events with the use of Harvoni (ledipasvir/sofosbuvir). The Division of Antiviral Products (DAVP) consulted the Division of Pharmacovigilance II (DPV II) to assess all adverse events in light of several supplements submitted by the sponsor to expand indications to liver transplant recipients with genotype 1 and 4 hepatitis C virus (HCV) infection, as well as patients with decompensated cirrhosis with genotype 1 HCV infection.

1.2 REGULATORY HISTORY

Ledipasvir/sofosbuvir (LDV/SOF) is a fixed-dose combination drug approved on October 10, 2014 for the treatment of chronic hepatitis C infection (CHC).¹ Ledipasvir is an inhibitor of the HCV NS5A protein, which is required for viral replication. Sofosbuvir is an NS5B polymerase inhibitor and a uridine nucleotide analog with activity against hepatitis C virus (HCV). It is a prodrug that gets converted to the active uridine triphosphate form (GS-461203) in hepatic cells and it subsequently acts to inhibit HCV replicon RNA replication.

LDV/SOF's efficacy has been established in subjects with HCV genotype 1. The dose regimen of LDV/SOF is one tablet (LDV 90 mg/SOF 400 mg) orally once daily with or without food. For the recommended treatment duration of LDV/SOF therapy, please refer to full prescribing information.

1.3 PRODUCT LABELING

The WARNINGS AND PRECAUTIONS section of the label warns of the risk of serious symptomatic bradycardia when LDV/SOF is coadministered with amiodarone. Additionally, the label warns of the interaction between LDV/SOF and potent P-gp inducers in the intestine (e.g., rifampin, St. John's wort) which can significantly decrease LDV/SOF plasma concentrations and may lead to a reduced therapeutic effect of LDV/SOF.

The most common adverse events ($\geq 10\%$) for LDV/SOF were fatigue and headache in subjects treated with 8, 12, or 24 weeks of LDV/SOF. Treatment-emergent laboratory abnormalities that were observed at a higher incidence in LDV/SOF-treated subjects than in placebo-treated subjects are bilirubin elevations and lipase elevations. For details on ADVERSE REACTIONS, please refer to sofosbuvir full prescribing information.¹

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

The FAERS database was searched with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of search	October 28, 2015
Time period of search	October 10, 2014 [^] - October 28, 2015
Product Terms	Ledipasvir, Ledipasvir/Sofosbuvir, Harvoni, Harvoni Access
Type of Search	Quick Query

* See Appendix A for description of the FAERS database.

[^] FDA Approval Date

2.1 DATA MINING SEARCH STRATEGY

A data mining analysis of FAERS was performed for this review using Empirica Signal[®] software using the strategy described in Table 2. See Appendix A for a description of data mining of FAERS using Empirica Signal.

Table 2. Data Mining Strategy to Identify PTs with EB05 Scores >2	
Data Refresh Date	September 20, 2015
Drug Names	Ledipasvir, ledipasvir/sofosbuvir
Run Name	Generic by PT with EB05 > 2
MedDRA Search Terms	All adverse events retrieved at the MedDRA PT level

3 RESULTS

The results section is organized in three parts: 1) an overview of total counts of FAERS reports 2) an overview of data mining findings, and 3) a hands-on review of adverse events that were unlabeled and reported in high frequency, or deemed concerning by the reviewer (i.e., dyskinesia, hypertensive crisis and cerebral hemorrhage, pancreatitis, severe cutaneous adverse reactions, anemia, renal failure, hepatic decompensation and failure)

3.1 FAERS OVERVIEW

For the FAERS overview, please note that these are total counts of FAERS reports. Report counts may include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse, etc.), miscoded reports, or unrelated reports. Reported outcomes for this section are the coded outcomes submitted to FDA; causality and the role of the product in the coded outcome have not been determined for this evaluation.

3.1.1

FAERS Search Results

The FAERS search on October 28, 2015 yielded 4,374 reports.

Table 3. Descriptive characteristics of FAERS Reports for LDV/SOF received by FDA between October 10, 2014 - October 28, 2015		
(N=4,374)*		
Sex	Male	2,346
	Female	1,864
	Unknown	164
Country of reporter	United States	3,640
	Foreign	706
	Null	28
Report type	Expedited	2,363
	Direct	961
	Periodic	1,050
Serious Outcomes[^]	Death	198
	Life-threatening	71
	Hospitalized	901
	Disability	50
	Congenital anomaly	1
	Other serious	1723

* May include duplicates

[^] Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. A report may have one or more outcome.

Table 4. Breakdown of FAERS Reports by age for LDV/SOF received by FDA between October 10, 2014 - October 28, 2015	
(N=4,374)*	
Age Group	Number of Reports* (US)
0 yrs- 16 yrs	7
17 yrs – 20 yrs	1
21 yrs – 30 yrs	47
31 yrs – 40 yrs	114
41 yrs – 50 yrs	369
51 yrs – 60 yrs	1319
61 yrs – 70 yrs	1047
71 yrs +	200
Unknown	1270

* May include duplicates

The most frequently reported MedDRA Preferred Terms (PTs) are shown in the tables below.

Table 5. Most Frequently Reported MedDRA PTs with N ≥ 45 for LDV/SOF, received by FDA between October 10, 2014 - October 28, 2015, sorted by decreasing number of FAERS reports per PT			
Total Number of Reports* = 4,374			
Row	MedDRA PT	Number of FAERS Reports	Labeled[^] (Yes/No), Location
1	Fatigue	693	Yes, AR
2	Headache	675	Yes, AR
3	Nausea	265	Yes, AR
4	Insomnia	213	Yes, AR
5	Diarrhea	200	Yes, AR
6	Drug Ineffective	196	No, U
7	Vomiting	143	No
8	Hepatitis C	124	No, IR
9	Anxiety	121	No
10	Dizziness	121	No
11	Rash	105	No
12	Dyspnea	99	No
13	Depression	96	No
14	Arthralgia	87	No
15	Drug Interaction	85	Yes, DI
16	Anemia	80	No
17	Hypertension	80	No
18	Asthenia	74	No
19	Pain	74	No
20	Decreased Appetite	73	No, DR
21	Pyrexia	70	No
22	Abdominal Pain	69	No, DR
23	Blood Pressure Increased	69	No
24	Constipation	69	No
25	Death	66	No
26	Blood Creatinine Increased	59	No
27	Dyspepsia	59	No
28	Abdominal Discomfort	58	No, DR
29	Confusional State	58	Yes, WP**
30	Malaise	58	Yes, WP**
31	Pain in Extremity	58	No
32	Ascites	56	No, DR
33	Pruritus	55	No
34	Hepatic Encephalopathy	54	No, DR
35	Acute Kidney Injury	53	No
36	Abdominal Pain Upper	52	No, DR

37	Fall	51	No
38	Hepatitis C Virus Test Positive	50	No, IR
39	Back Pain	48	No
40	Feeling Abnormal	48	No, U
41	Nasopharyngitis	48	No
42	Pneumonia	48	No
43	Chest Pain	47	Yes, WP**
44	Abdominal Distention	46	No
45	Myalgia	46	No

* A report may contain more than one preferred term

** Confusion, malaise, and chest pain are part of the bradycardia warning when LDV/SOF is used in combination with amiodarone

^ Definitions: WP = Warnings/Precautions, AR = Adverse Reactions, DI = Drug Interactions, IR = Indication-related, U=Uninformative

Table 6. Most Frequently Reported MedDRA PTs with N ≥ 30 from FAERS Reports with Serious Outcomes for LDV/SOF, received by FDA between October 10, 2014 - October 28, 2015, sorted by decreasing number of FAERS reports per PT

Total Number of Reports* = 2,310

Row	MedDRA PT	Number of FAERS Reports	Labeled [^] (Yes/No), Location
1	Headache	216	Yes, AR
2	Fatigue	196	Yes, AR
3	Drug Ineffective	192	No, U
4	Hepatitis C	124	No, IR
5	Nausea	114	Yes, AR
6	Vomiting	86	No
7	Anemia	74	No
8	Dyspnea	73	No
9	Diarrhea	72	Yes, AR
10	Insomnia	72	Yes, AR
11	Death	66	No
12	Dizziness	66	No
13	Drug Interaction	64	Yes, DI
14	Asthenia	59	No
15	Hypertension	59	No
16	Ascites	56	No, DR
17	Abdominal Pain	54	No, DR
18	Acute Kidney Injury	53	No
19	Hepatic Encephalopathy	53	No, DR
20	Blood Creatinine Increased	51	No
21	Pneumonia	48	No
22	Pyrexia	48	No
23	Malaise	47	Yes, WP

24	Decreased Appetite	45	No, DR
25	Fall	45	No
26	Blood Pressure Increased	42	No
27	Confusional State	41	Yes, WP
28	Depression	37	No
29	Chest Pain	36	Yes, WP
30	Encephalopathy	35	No, DR
31	Arthralgia	34	No
32	Hepatic Cirrhosis	34	Yes, IR
33	Anxiety	32	No
34	Pain	32	No
35	Pain in Extremity	32	No
36	Rash	31	No
37	Renal Failure	31	No
38	Gastrointestinal Hemorrhage	30	No

* A report may contain more than one preferred term

** Confusion, malaise, and chest pain are part of the bradycardia warning when LDV/SOF is used in combination with amiodarone

^ Definitions: WP = Warnings/Precautions, AR = Adverse Reactions, DI = Drug Interactions, IR = Indication-related, U=Uninformative

Table 7. MedDRA PTs with N ≥ 5 from FAERS Reports with Fatal Outcomes for LDV/SOF, received by FDA between October 10, 2014 - October 28, 2015, sorted by decreasing number of FAERS reports per PT
Total Number of Reports* = 198

Row	MedDRA PT	Number of FAERS Reports	Labeled [^] (Yes/No) Location
1	Death	66	No
2	Cardiac Arrest	13	No
3	Ascites	12	No, DR
4	Multi-Organ Failure	11	No
5	Sepsis	11	No
6	Septic Shock	10	No
7	Abdominal Pain	9	No, DR
8	Hepatic Cirrhosis	9	Yes, IR
9	Hepatic Encephalopathy	9	No, DR
10	Hepatic Failure	9	No, DR
11	Respiratory Failure	9	No
12	Vomiting	9	No
13	Malaise	8	Yes, WP ^{**}
14	Cardiac Disorder	7	No
15	Gastrointestinal Hemorrhage	7	No
16	Cerebral Hygroma	6	No
17	Completed Suicide	6	No

18	Diarrhea	6	Yes, AR
19	Disorientation	6	No, DR
20	Dyskinesia	6	No
21	Fall	6	No
22	Hallucination	6	No
23	Cerebral Hemorrhage	5	No
24	Drug Interaction	5	Yes, DI
25	Fatigue	5	Yes, AR
26	Myocardial Infarction	5	No
27	Pneumonia	5	No

* A report may contain more than one preferred term

** Malaise is part of the bradycardia warning when LDV/SOF is used in combination with amiodarone

^ Definitions: W/P = Warnings/Precautions, AR = Adverse Reactions, IR = Indication-related, DR= Disease Related

Designated Medical Events (DMEs) are events that are inherently medically important and often product-related. OSE created the DME list for working purposes; it has no regulatory significance. See Appendix B for a list of OSE’s Designated Medical Events.

Table 8. MedDRA DME-related PTs with N ≥ 10 from FAERS Reports for LDV/SOF, received by FDA between October 10, 2014 - October 28, 2015, sorted by decreasing number of FAERS reports per PT			
Total Number of Reports* = 329			
Row	MedDRA DME-related PT	Number of FAERS Reports	Labeled[^] (Yes/No) Location
1	Hepatic Encephalopathy	54	No, DR
2	Acute Kidney Injury	53	No
3	Renal Failure	31	No
4	Hepatic Failure	24	No, DR
5	Ascites	22	No, DR
6	Fatigue	21	Yes, AR
7	Seizure	20	No
8	Renal Impairment	19	No
9	Headache	18	Yes, AR
10	Blood Creatinine Increased	16	No
11	Dizziness	16	Yes, WP ^{**}
12	Confusional State	15	No, DR
13	Nausea	14	Yes, AR
14	Dehydration	13	No
15	Diarrhea	13	Yes, AR
16	Dyspnea	13	No
17	Fall	13	No
18	Pancreatitis	13	No
19	Anemia	12	No
20	Decreased Appetite	12	No, DR

21	Drug Interaction	12	Yes, DI
22	Pancreatitis Acute	12	No
23	Pancytopenia	11	No
24	Respiratory Failure	11	No
25	Vomiting	11	No
26	Hepatic Cirrhosis	10	Yes, IR
27	Liver Transplant	10	No
28	Rhabdomyolysis	10	No
29	Septic Shock	10	No

* A report may contain more than one preferred term

** Dizziness is part of the bradycardia warning when LDV/SOF is used in combination with amiodarone

^ Definitions: W/P = Warnings/Precautions, AR = Adverse Reactions, IR = Indication-related

3.2 DATA MINING

Table 9 lists the disproportionality measures, ranked by descending EB05, for MedDRA PTs associated with LDV/SOF. An EB05 score >2 is indicative of a potential signal between a drug and adverse event pair.

PT	N	EBGM	EB05	EB95	Labeled (Yes/No), and Other Category*
Hepatitis C virus test positive	42	92.016	70.821	117.941	Yes, IR
Hepatitis C	100	19.037	16.093	22.387	Yes, IR
Hepatic encephalopathy	39	13.855	9.853	18.465	No, DR
Glomerular filtration rate decreased	21	7.287	4.894	11.094	No
Encephalopathy	31	6.469	4.758	8.689	No, DR
Ascites	43	5.583	4.318	7.129	No, DR
Headache	621	4.508	4.219	4.813	Yes, AR
Hepatic cirrhosis	27	5.819	4.196	7.932	Yes, IR
Fatigue	629	3.936	3.684	4.2	Yes, AR
Esophageal varices haemorrhage	9	6.288	3.275	14.687	No, DR
Blood bilirubin increased	32	4.364	3.24	5.776	Yes, AR
Accidental overdose	24	4.462	3.161	6.157	No
Energy increased	12	4.726	2.888	7.433	No
Blood creatinine increased	46	3.525	2.752	4.46	No
Liver transplant	9	4.904	2.749	8.435	No
Insomnia	192	2.957	2.622	3.324	Yes, AR
Hepatic pain	9	4.514	2.55	7.606	No
Drug interaction	72	3.096	2.542	3.741	Yes, DI
Ammonia increased	9	4.321	2.447	7.242	No, DR
Cardiotoxicity	7	4.562	2.359	8.466	No
Varices oesophageal	7	4.293	2.239	7.767	No, DR
Portal vein thrombosis	7	4.273	2.23	7.721	No
Irritability	41	2.802	2.156	3.593	No
Haemoglobin decreased	5	5.513	2.13	24.229	No

Dermatitis bullous	8	3.78	2.073	6.471	No
Hepatic failure	19	3.005	2.04	4.3	No, DR
Dyspepsia	53	2.549	2.025	3.175	No
Bradycardia	23	2.85	2.005	3.955	Yes, WP

N= number of reports coded with a preferred term in that HLT, EBGM=Empirical Bayes Geometric Mean, EB05=lower 90% confidence limit for the EBGM, EB95= upper 90% confidence limit for the EBGM.

*Other Categories: WP = Warnings and Precautions, DI=Drug Interaction, DR=Disease-related, IR=Indication-related

3.3 HANDS-ON REVIEW OF ADVERSE EVENTS

Based on the FAERS and datamining search results and a thorough evaluation of the PTs retrieved, adverse events that were unlabeled and reported in high frequency or deemed concerning by the reviewer (i.e., dyskinesia, hypertensive crisis and cerebral hemorrhage, pancreatitis, severe cutaneous adverse reactions, anemia, renal failure, hepatic decompensation and failure) are further discussed below. Duplicate reports were excluded which may have led to a discrepancy in case numbers between the tables above and the discussion of individual adverse events below.

Adverse Event of Interest: Dyskinesia

The risk of dyskinesia is not listed in the LDV/SOF label. This unlabeled AE was further explored in order to assess cases of dyskinesia reported after drug approval.

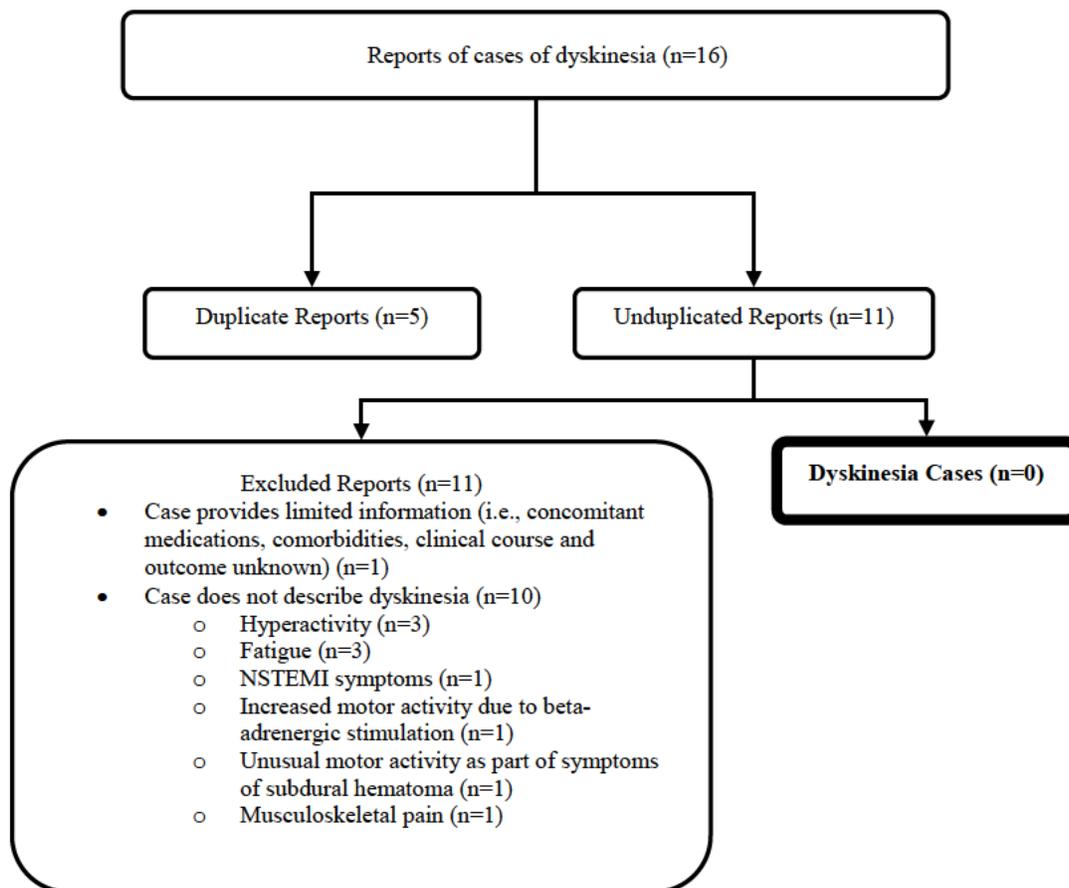
The FAERS database was searched with the strategy described in Table 10.

Date of search	November 6, 2015
Time period of search	October 10, 2014 [^] - November 6, 2015
Product Terms	Harvoni, Harvoni access, ledipasvir, ledipasvir/sofosbuvir
Type of Search	Quick Query
Search Parameters	HLT: Dyskinesias and Movement Disorders NEC

* See Appendix A for description of the FAERS database.

[^] FDA Approval Date

Figure 1. Selection of Cases of Dyskinesia with LDV/SOF



The FAERS search yielded no cases.

Adverse Event of Interest: Hypertensive Crisis and Cerebral Hemorrhage

The risk of hypertensive crisis and cerebral hemorrhage is not listed in the LDV/SOF label. Hypertensive crisis and cerebral hemorrhage were evaluated because they are severe outcomes that may result from hypertension. The PTs “hypertension” and “increased blood pressure” were reported in high frequency in FAERS. These severe unlabeled adverse events were further explored in order to assess cases reported after drug approval. Of note, the sponsor evaluated both pre- and post-approval cases of hypertensive crisis and cerebral hemorrhage with SOF on September 26, 2015 as part of an FDA Request for Information Response.² The sponsor concluded that there was insufficient evidence of a causal relationship from the cases in their database and there is no convincing evidence that SOF-containing regimens are associated with hypertensive crisis or cerebrovascular accident.

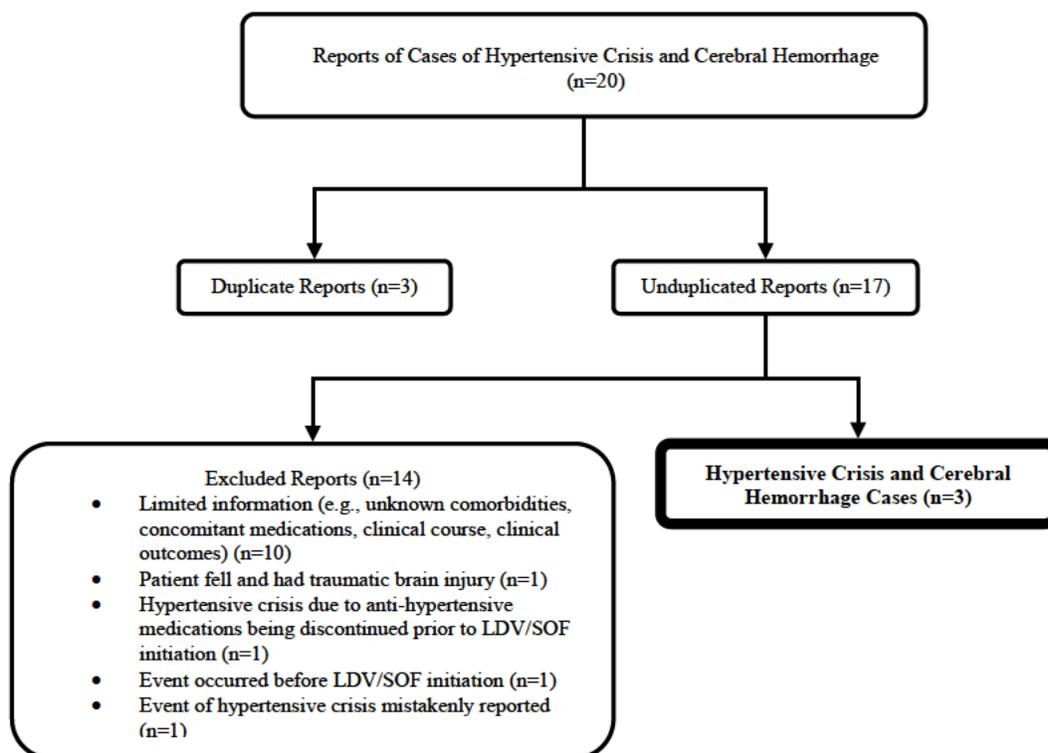
The FAERS database was searched with the strategy described in Table 11.

Table 11. FAERS Search Strategy*	
Date of search	November 6, 2015
Time period of search	October 10, 2014 [^] - November 6, 2015
Product Terms	Harvoni, Harvoni access, ledipasvir, ledipasvir/sofosbuvir
Type of Search	Quick Query
Search Parameters	PT: Hypertensive crisis, Cerebral Hemorrhage

* See Appendix A for description of the FAERS database.

[^] FDA Approval Date

Figure 2. Selection of Cases of Hypertensive Crisis and Cerebral Hemorrhage with LDV/SOF



Hypertensive Crisis and Cerebral Hemorrhage Cases

FAERS Case# 11290142 describes a 27-year-old female patient with a history of hypotension who experienced hypertensive crisis leading to hospitalization after 18 days of LDV/SOF. The patient's comorbidities included bladder spasms, depression, anxiety, constipation, reflux, and a recent tick bite. Concomitant medications included mirabegron, fluoxetine, linaclotide, dexlansoprazole, hyoscyamine, and drospirenone/ethinyl estradiol. Her symptoms on admission

were profuse diaphoresis, palpitations, and rash all over her body associated with mild shortness of breath, which began to worsen on and off. Her blood pressure (BP) was 160/110 and she was "a bit" tachycardic. She was administered propranolol but her symptoms worsened. She was admitted to the intensive care unit and was treated with hydralazine, famotidine, diphenhydramine, ondansetron, labetalol, amlodipine, carvedilol, ferrous gluconate. The patient's BP, flushing, and diaphoresis improved. No renal or cardiac cause was identified for her elevated BP. Five days later, her BP improved to 143/88 and that patient was discharged in stable condition with a recommendation for follow-up with her primary care physician and nephrology as well as outpatient sleep study evaluation for sleep apnea. The patient also received doxycycline due to a recent tick bite. The action taken with HCV treatment is unknown. The patient's BP values over time are listed in the table below. *Reviewer's Comments: This case is confounded by the patient's fluctuating blood pressure prior to starting HCV treatment (see table 12 below) and concomitant use of mirabegron (labeled for increases in blood pressure under "Warnings and Precautions" section, medication started approximately 3 months prior to HCV treatment). Of note, the sponsor assessed this case to be confounded by pre-existing depression, underlying anxiety, and fluctuating blood pressure 9 months prior to starting LDV/SOF.² However, the occurrence of hypertensive urgency requiring intensive care unit stay after 18 days of LDV/SOF treatment supports a temporal association.*

Table 12. Patient's BP Values over Time for FAERS Case# 11290142

	Pre-treatment					Post-treatment		
	9/6/2014	10/24/2014	12/12/2014	1/12/2015	5/1/2015	7/2/2015	7/6/2015	7/10/2015
BP (mmHg)	132/90	105/60	148/100	145/90	112/66	122/68	160/110 148/100	143/88

FAERS Case# 11309606 describes a 53-year-old male with comorbidities of phantom pain, chronic obstructive pulmonary disease (COPD), insomnia, depression, hepatic steatosis, dyspnea, osteosarcoma, meniscus injury and operation. Of note, the patient did not have a pre-existing diagnosis of hypertension prior to HCV treatment and his BP measurements are shown in the table 13 below (this information was gathered from the sponsor's request for information response as BP measurements were not included in the FAERS report)². At week 5 of LDV/SOF treatment, he was started on hydrochlorothiazide (HCTZ) for hypertension but a week later developed dizziness and weakness, which required hospitalization as he was noted to have hyponatremia and hypertensive urgency. The patient was started on atenolol for hypertension treatment, which led to improvement. HCTZ was discontinued as it was thought to be the cause of the hyponatremia. LDV/SOF was discontinued during the 3 day hospitalization but restarted at time of discharge. Concomitant medications included oxazepam, hydromorphone, tiotropium, and fluticasone/vilanterol. *Reviewer's Comments: This case is confounded by the patient's elevated blood pressure prior to treatment. Of note, the sponsor assessed this case to be confounded by undiagnosed pre-existing hypertension at baseline.² However, by week 12, his blood pressure was again elevated despite antihypertensive treatment suggesting an association between administration of LDV/SOF and onset or worsening of hypertension.*

Table 13. Patient’s BP Values over Time for FAERS Case# 11309606

	Screening	Baseline	Week 1	Week 2	Week 4	Week 8	Week 12
BP (mmHg)	134/96	120/86	133/93	146/96	129/99	126/90	135/87

FAERS Case# 11511720 describes a 73-year-old cirrhotic with mild chronic bronchitis and benign prostatic hyperplasia (BPH) who complained of fatigue and nonspecific dizziness since initiation of Harvoni. The patient had a progressive increase in BP from his baseline systolic of 110 mmHg to 140-150 mmHg. Forty-five days after initiation of LDV/SOF, the patient went to the primary care physician with sudden headache and BP of 220/110 mmHg. The patient was diagnosed with subarachnoid hemorrhage associated with posterior communicating aneurysm and hypertensive crisis. Of note, the patient was previously normotensive. The patient was hospitalized and treated with enalapril. After four days, the patient had persistent pain, sleepiness, and BP of 160-170/100 mmHg. At the time of reporting the patient was hospitalized, conscious with neurological focus, and pending arteriography and therapeutic decision, still hospitalized. It is unknown what action was taken with HCV treatment. *Reviewer’s Comments: This case is confounded by the patient’s age and lack of details on concomitant medications. Additionally, the full clinical course is not described since the events were ongoing at the time of the report. However, there is a temporal association between administration of LDV/SOF and hypertensive crisis and cerebrovascular accident.*

Adverse Event of Interest: Pancreatitis

The risk of lipase elevations is listed under ADVERSE REACTIONS but the risk of pancreatitis is not listed in the LDV/SOF label. This unlabeled adverse event was further explored in order to assess cases of pancreatitis reported after drug approval. Of note, DPV II assessed the risk of pancreatitis with LDV/SOF in a six months post-marketing review.³ The LDV/SOF cases of pancreatitis found contained limited information (i.e., unknown comorbidities, concomitant medications, clinical course, clinical outcomes) or had a more likely cause for pancreatitis (i.e., alcohol abuse).

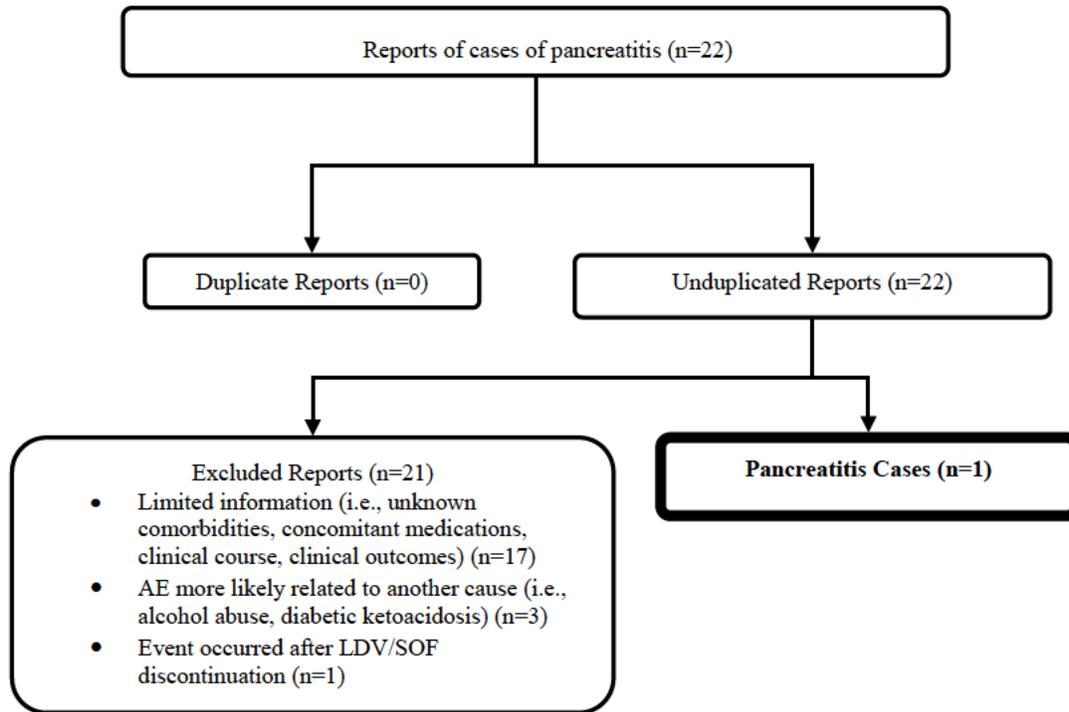
The FAERS database was searched with the strategy described in Table 14.

Table 14. FAERS Search Strategy*	
Date of search	November 6, 2015
Time period of search	April 7, 2015 [^] - November 6, 2015
Product Terms	Harvoni, Harvoni access, ledipasvir, ledipasvir/sofosbuvir
Type of Search	Quick Query
Search Parameters	HLT: Acute and chronic pancreatitis

* See Appendix A for description of the FAERS database.

[^] Date cutoff for last review evaluating pancreatitis³

Figure 3. Selection of Cases of Pancreatitis with LDV/SOF



FAERS Case# 11309143 describes a 63-year-old male patient with a history of osteoarthritis, hypertension, and GERD who experienced acute pancreatitis (lipase 1273 U/L), creatinine elevation [creatinine 250 (units unknown)], and orthostatic hypotension after 37 days of treatment with LDV/SOF. Concomitant medications included diclofenac/misoprostol, candesartan, pantoprazole, and pregabalin. The patient was hospitalized and treated with intravenous fluids and pain medications. The patient improved and was discharged two days later. LDV/SOF was discontinued at the time of the events because the reporter believed the HCV treatment was the culprit of the events. Of note, the patient had no previous episodes of pancreatitis, no history of hypertriglyceridemia, hypercalcemia, autoimmune disease, and denied alcohol use. *Reviewer's Comments: This case is confounded by the concomitant use of drugs labeled for pancreatitis [i.e., diclofenac/misoprostol (pancreatitis labeled under "Adverse Reactions"), pregabalin (pancreatitis labeled under "Adverse Reactions")]. However, there is a temporal association between administration of LDV/SOF and pancreatitis.*

Adverse Event of Interest: Severe Cutaneous Adverse Reactions

The risk of rash or severe cutaneous adverse reactions is not listed in the LDV/SOF label. DPV II assessed the risk of severe cutaneous adverse reactions with LDV/SOF in a six months post-marketing review.³ There were four cases reporting rash that supported a new safety signal based on temporal association. The events included erythema multiforme and rash with blisters on various body areas (i.e., hands, wrists, armpits, buttocks, knees, genital area) occurring within a

median of seven days of treatment initiation. There were no cases of SJS or TEN reported. Additionally, the sponsor performed a cumulative review of postmarketing serious cases of rash and label changes are pending to add the risk of skin rash to the “Postmarketing Experience” section.⁴

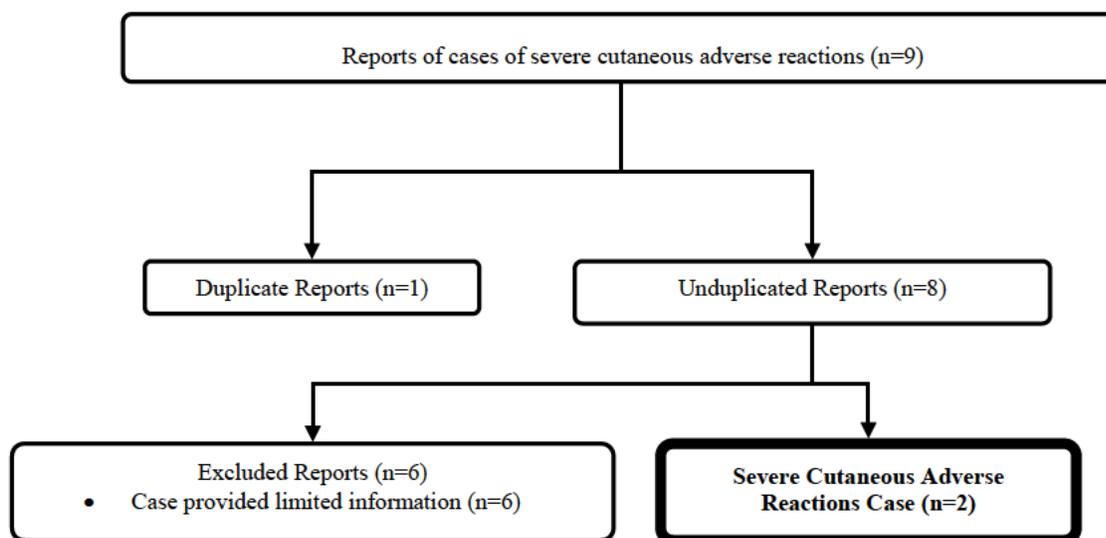
The FAERS database was searched with the strategy described in Table 15.

Date of search	November 6, 2015
Time period of search	April 7, 2015 [^] - November 6, 2015
Product Terms	Harvoni, Harvoni access, ledipasvir, ledipasvir/sofosbuvir
Type of Search	Quick Query
Search Parameters	SMQ: Severe cutaneous adverse reactions (SMQ) SMQ Scope: Narrow

* See Appendix A for description of the FAERS database.

[^] Date cutoff for last review evaluating severe cutaneous adverse reactions³

Figure 4. Selection of Cases of Severe Cutaneous Adverse Reactions (SMQ) with LDV/SOF



The two cases described erythema multiforme and small skin necroses on arms after 39 days and 44 days of LDV/SOF treatment, respectively. The severity of these cases was consistent with what was identified in the previous 6 months review.³ There were no cases of SJS or TEN reported.

Adverse Event of Interest: Anemia

The risk of anemia is not listed in the LDV/SOF label and this PT was noted on the overview of total counts of FAERS reports. Due to the complexity of assessing this AE in patients with HCV, this AE will be discussed in a separate DPV II review.

Adverse Event of Interest: Renal Failure

The risk of renal failure is not listed in the LDV/SOF label. There were several PTs related to renal dysfunction noted (e.g., blood creatinine increased, acute kidney injury, renal failure, renal impairment, glomerular filtration rate decreased) and due to the complexity of assessing this AE in patients with HCV, this AE will be discussed in a separate DPV II review.

Adverse Event of Interest: Hepatic decompensation and failure

The risk of hepatic decompensation and failure are not listed in the LDV/SOF label. There were several PTs related to hepatic dysfunction noted (e.g., hepatic failure, liver transplant, hepatic encephalopathy) and due to the complexity of assessing this AE in patients with HCV, this AE will be discussed in a separate DPV II review.

4 DISCUSSION

A review of the most frequently reported PTs for all reports, deaths, and DMEs identified PTs that were labeled (e.g., headache, fatigue, nausea, insomnia, diarrhea, malaise) or liver disease related (e.g., encephalopathy, hepatic failure, ascites).

There were three cases of hypertensive crisis that support a drug-event association based on temporal association. One patient also experienced a subarachnoid hemorrhage. However, the cases were confounded by elevated BP at baseline and concomitant medications and comorbidities. A literature review did not find any published information supporting a relationship between SOF or SOF/LDV and hypertensive crisis or cerebral hemorrhage. Due to the small number of cases and the confounding factors, there is insufficient information to support a new safety signal. DPV II will continue to monitor for cases of hypertensive crisis and cerebral hemorrhage reported with SOF and SOF/LDV.

One case of pancreatitis with a temporal association to LDV/SOF was identified. However, the case was confounded by concomitant medications associated with pancreatitis. Due to only having a single case and the confounding factors, a definitive causal relationship between LDV/SOF and pancreatitis cannot be made at this time. DPV II will continue to monitor for cases of pancreatitis reported with LDV/SOF use.

The severity of the cases describing severe cutaneous adverse reactions was consistent with what was identified in the previous 6 months review.³ There were no cases of SJS or TEN reported.

Cases reporting the unlabeled events of anemia, renal failure, and hepatic decompensation and failure will be assessed in a separate DPV II review. Hepatic decompensation and failure in

patients with HCV infection are not unexpected; however, given the concerns of hepatotoxicity with other direct acting antivirals, such as simeprevir and Viekira Pak, we plan to evaluate this signal further.

5 CONCLUSION

No new safety signals were identified in this review of FAERS post-marketing reports of LDV/SOF use.

6 RECOMMENDATIONS

DPV II will continue to monitor for all adverse events associated with the use of LDV/SOF.

7 REFERENCES

1. (Harvoni[®]) [package insert]. Foster City, CA 94404: Gilead Sciences, Inc.; 2014.
2. Response to FDA Request for Information Comments Dated August 20, 2015. Module 1.11.3, NDA 204671. Gilead Sciences, Inc. September 16, 2015.
3. Jason M. All adverse events with LDV/SOF use 6 months post-marketing. RCM 2015-1018. Completed May 15, 2015.
4. Response to FDA Request for Information Comments Dated June 5, 2015. Module 1.11.3, NDA 205834. Gilead Sciences, Inc. July 7, 2015.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Data Mining of FAERS using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. "Data mining" refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to

FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGGM scores

8.2 APPENDIX B. LIST OF OSE DESIGNATED MEDICAL EVENTS AND ASSOCIATED MEDDRA PREFERRED TERMS

Designated Medical Event	MedDRA Preferred Terms
Acute pancreatitis	Pancreatic necrosis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising, Pancreatitis
Acute respiratory failure	Acute respiratory distress syndrome, Acute respiratory failure, Respiratory failure
Agranulocytosis	Agranulocytosis, Febrile neutropenia, Neutropenia
Amyotrophic lateral sclerosis	Amyotrophic lateral sclerosis
Anaphylaxis and anaphylactoid reactions	Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction, Anaphylactoid shock
Aplastic anemia	Aplasia pure red cell, Aplastic anemia, Bone marrow failure
Blind	Blindness, Blindness transient, Blindness unilateral, Optic ischaemic neuropathy, Sudden visual loss
Colitis ischaemic	Colitis ischaemic, Intestinal infarction
Congenital anomalies	Congenital anomaly
Deaf	Deafness bilateral, Deafness neurosensory, Deafness permanent, Deafness transitory, Deafness unilateral, Deafness, Sudden hearing loss
Diss. intravascular coagulation	Disseminated intravascular coagulation
Endotoxic shock, confirmed or suspected	Endotoxic shock, Septic shock
Haemolysis	Haemoglobinaemia, Haemoglobinuria, Haemolysis, Haptoglobin decreased, Intravascular haemolysis
Hemolytic anemia	Coombs negative haemolytic anaemia, Coombs positive haemolytic anaemia, Haemolytic anaemia
Liver failure	Acute hepatic failure, Hepatic encephalopathy, Hepatic failure, Subacute hepatic failure
Liver necrosis	Hepatitis acute, Hepatitis fulminant, Hepatic necrosis
Liver transplant	Liver transplant
Neuroleptic malignant syndrome	Neuroleptic malignant syndrome
Pancytopenia	Pancytopenia
Progressive multifocal leukoencephalopathy	Progressive multifocal leukoencephalopathy
Product infectious disease transmission	Product contamination microbial Transfusion-transmitted infectious disease Transmission of an infectious agent via a medicinal product
Pulmonary fibrosis	Pulmonary fibrosis
Pulmonary hypertension	Cor pulmonale, Pulmonary hypertension
Renal failure	Renal failure, Renal failure acute, Renal impairment
Rhabdomyolysis	Rhabdomyolysis
Seizure	Convulsion, Epilepsy, Grand mal convulsion
Serotonin syndrome	Serotonin syndrome
Stevens-Johnson syndrome	Erythema multiforme, Stevens-Johnson syndrome
Sudden death	Sudden cardiac death, Sudden death
Suicide	Completed suicide

Torsade de Pointes	Torsade de pointes
Toxic epidermal necrolysis	Dermatitis exfoliative, Toxic epidermal necrolysis
TTP	Thrombotic thrombocytopenic purpura
Ventricular fibrillation	Ventricular fibrillation

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/s/

MIHAELA P JASON
12/04/2015

KELLY Y CAO
12/04/2015

STEVEN C JONES
12/04/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: November 5, 2015
Requesting Office or Division: Division of Antiviral Products (DAVP)
Application Type and Number: NDA 205834/S-07 through 09
Product Name and Strength: Harvoni
(ledipasvir and sofosbuvir), Tablets
90 mg/400 mg
Product Type: Multi-ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Gilead Sciences, Inc
Submission Date: August 26, 2015
OSE RCM #: 2015-2025
DMEPA Primary Reviewer: Mónica Calderón, PharmD, BCPS
DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

Gilead Sciences, Inc. submitted three efficacy supplements (S-07 through S-09) in support of proposed changes to the approved full prescribing information (FPI) to expand the potential benefit of Harvoni to the following subpopulations: liver transplant recipients with Genotype 1 HCV infection (S-07), liver transplant recipients with Genotype 4 HCV infection (S-08), and patients with decompensated cirrhosis with Genotype 1 HCV infection (S-09). Thus, the Division of Antiviral Products (DAVP) requested DMEPA evaluate the Sponsor's revised FPI.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Gilead Sciences, Inc. is proposing to expand the indications and use of Harvoni to include liver transplant recipients with Genotype 1 and 4 HCV infection and patients with decompensated cirrhosis with Genotype 1 HCV. DMEPA performed a risk assessment of the proposed FPI to identify deficiencies that may lead to medication errors and areas of improvement.

FPI, Dosage and Administration Section

Preliminary labeling issues were identified and communicated to the Sponsor at the Midcycle Communication meeting for NDA 205834/S-02 through 06 on September 1, 2015. The Sponsor implemented DMEPA's recommendations in the revised PI submitted September 3, 2015 (See Appendix G) for S-02 through 06.¹ The revisions made to Table 1 clearly delineated the treatment options for patients based on genotype.

¹ Calderon, M. Label and Labeling Review for Harvoni NDA 205834. Silver Spring (MD): FDA,

We evaluated the revised Dosage and Administration section for the current efficacy supplements which includes recommendations for the treatment of liver transplant recipients with Genotype 1 and 4 HCV infection and patients with decompensated cirrhosis with Genotype 1 HCV and we find the proposed changes acceptable. However, the changes made for S-02 through 06 are not implemented in this FPI since the changes were made after submission of S-07 through 09. For consistency and clarity between supplements, we provide recommendations in Section 4.1.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes the Sponsor's proposal for revisions to the Dosage and Administration section of the FPI to include treatment of liver transplant recipients with Genotype 1 and 4 HCV infection and patients with decompensated cirrhosis with Genotype 1 HCV are acceptable. However, we provide recommendations in Section 4.1 for consistency and clarity with revisions made during review of submission S-02 through 06.

4.1 RECOMMENDATIONS FOR THE DIVISION

DMEPA recommends implementing the changes made to the Dosage and Administration section during S-02 through 06 (Appendix G).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

CDER, OSE, DMEPA (US); 2015 09 16. RCM No.: 2015-1199.

Table 2 presents relevant product information for Harvoni that Gilead Sciences, Inc. submitted on August 26, 2015.

Table 2. Relevant Product Information for Harvoni	
Initial Approval Date	October 10, 2014
Active Ingredient	ledipasvir and sofosbuvir
Indication	(b) (4)
Route of Administration	Oral
Dosage Form	Tablet
Strength	90 mg/400 mg
Dose and Frequency	One tablet once daily with or without food
How Supplied	Bottle of 28 tablets with child-resistant closure
Storage	Room temperature below 30°C (86°F)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On October 27, 2015, we searched the L:drive and AIMS using the terms, Harvoni to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified four previous reviews^{2,3,4,5}, and we confirmed that our previous recommendations were implemented.

² Calderon, M. Post-marketing Review for Harvoni NDA 205834. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 10 07. RCM No.: 2015-1105-1.

³ Calderon, M. Label and Labeling Review for Harvoni NDA 205834. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 09 16. RCM No.: 2015-1199.

⁴ Calderon, M. Post-marketing Review for Harvoni NDA 205834. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 08 19. RCM No.: 2015-1105.

⁵ Calderon, M. Label and Labeling Review for Harvoni NDA 205834. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 07 10. RCM No.: 2014-353.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On October 27, 2015, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care Nursing Community
Search Strategy and Terms	Match Exact Word or Phrase: Harvoni

D.2 Results

No cases were identified.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁶ along with postmarket medication error data, we reviewed the following Harvoni labels and labeling submitted by Gilead Sciences, Inc. on November 3, 2015.

- FPI

G.2 Label and Labeling Images

2 DOSAGE AND ADMINISTRATION



⁶ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.



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/s/

MONICA M CALDERON
11/06/2015

BRENDA V BORDERS-HEMPHILL
11/06/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 205834 BLA#	NDA Supplement #: S-7, 8, & 9 BLA Supplement #: S-	Efficacy Supplement Category: <input checked="" type="checkbox"/> New Indication (SE1) Supplement-8 <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input checked="" type="checkbox"/> New Patient Population (SE5) Supplement <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: Harvoni Established/Proper Name: ledipasvir and sofosbuvir Dosage Form: Tablet Strengths: 90/400 mg		
Applicant: Gilead Sciences, Inc. Agent for Applicant (if applicable): n/a		
Date of Application: August 26, 2015 Date of Receipt: August 26, 2015 Date clock started after UN: n/a		
PDUFA Goal Date: February 26, 2016		Action Goal Date (if different): n/a
Filing Date: October 25, 2015		Date of Filing Meeting: September 25, 2015
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Supplement 7 – Treatment of liver transplant recipients with Genotype 1 HCV infection. Supplement 8 – Treatment of liver transplant recipients with Genotype 4 HCV infection. Supplement 9 – Treatment of patients with decompensated cirrhosis with Genotype 1 HCV infection.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the “505(b)(2) Assessment” review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
The application will be a priority review if:	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> • <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i> • <i>The product is a Qualified Infectious Disease Product (QIDP)</i> • <i>A Tropical Disease Priority Review Voucher was submitted</i> • <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i> 	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input checked="" type="checkbox"/> PMR response: <input checked="" type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): Ledipasvir/Sofosbuvir Fixed-Dose Combination IND 115268, Sofosbuvir IND 106739

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also,</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		3 user fees paid
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment

Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes , answer the bulleted questions below:	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].	<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>				
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm	<input type="checkbox"/>	<input type="checkbox"/>		
If yes , please list below:				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>				
Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>				
NDA/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes , # years requested: 3				

<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Supplement 8, for transplant patients with genotype 4 HCV triggers PREA, but, supplement 6 is under review ^{(b) (4)}

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

Version: 7/10/2015

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<i>(including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Dated December 30, 2013
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	iPSP
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<u>BPCA:</u>				
Is this submission a complete response to a pediatric Written Request?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

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If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Has a review of the available pregnancy and lactation data been included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Labeling in PLLR format was requested and submitted by sponsor on 9/2/15
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult 9/4/15
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult 9/4/15
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult 9/4/15
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	OSI/DGCPC Consult – Request for Clinical Inspections
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 25, 2015

BACKGROUND: Gilead Sciences, Inc. has submitted three efficacy supplements (7, 8, & 9) seeking to expand the potential benefit of Harvoni (ledipasvir and sofosbuvir). Two Phase 2 studies (SOLAR-1) and (SOLAR-2) included in the application support the safety and efficacy of Harvoni plus ribavirin for 12 weeks in patients with HCV infection who are posttransplantation with compensated liver disease (genotype 1 and genotype 4 HCV) as well as patients with decompensated liver disease (genotype 1 HCV), regardless of transplantation status. The SOLAR-1 study also fully addresses Postmarketing Requirement 2780-7 which requires the final report and datasets 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).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Christian P. Yoder	Y
	CPMS/TL:	Karen Winestock	Y
Cross-Discipline Team Leader (CDTL)	Poonam Mishra		Y
Division Director/Deputy	Debra Birnkrant/Jeffrey Murray		Y
Office Director/Deputy	n/a		
Clinical	Reviewer:	Charu Mullick	Y
	TL:	Kim Struble	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Lisa Naeger	Y
	TL:	Julian O’Rear	Y

Clinical Pharmacology	Reviewer:	Jenny Zheng Jeffrey Florian	Y N
	TL:	Shirley Seo	N
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Wen Zheng	Y
	TL:	Greg Soon	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Christopher Ellis	Y
	TL:	Hanan Ghantous	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Stephen Miller	N
	RBPM:	Florence Aisida	N
• Drug Substance	Reviewer:		
• Drug Product	Reviewer:		
• Process	Reviewer:		
• Microbiology	Reviewer:		
• Facility	Reviewer:		
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Morgan Walker	N
	TL:	Barbara Fuller	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Kemi Asante	N
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Monica Calderon	Y
	TL:	Vicky Borders-Hemphill	N
OSE/Division of Pharmacovigilance	Reviewer:		
	TL:	Kelly Cao	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Antoine el Hage	N
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Discipline ”	Reviewer:		
	TL:		
Other attendees – OND ADRA	Stacy Min, PharmD, Associated Director for Labeling		Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505 b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p> 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> No comments

<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: This drug is not first in its class
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>New Molecular Entity (NDAs only)</u></p> <ul style="list-style-type: none"> Is the product an NME? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Division Director: Debra Birnkrant, MD	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 11/23/15	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTION ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTIAN P YODER
10/09/2015

KAREN D WINESTOCK
10/09/2015