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RESEARCH**

APPLICATION NUMBER:

205834Orig1s000

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 #	NDA 205834
Product Name:	Ledipasvir/sofosbuvir

PMR/PMC Description: Submit an interim study report and datasets for GS-US-334-0122

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>completed</u>
	Study/Trial Completion:	<u>07/31/2017</u>
	Final Report Submission:	<u>07/31/2018</u>
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/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

The ongoing trial GS-US-248-0122, entitled, “A Long Term Follow-up Registry for Subjects Who Achieve a Sustained Virologic Response to Treatment in Gilead-Sponsored Trials in Subjects with Chronic Hepatitis C Infection”, with the three year follow-up data from: GS-US-337-0102 (ION-1), GS-US-337-0109 (ION-2), GS-US-337-0108 (ION-3) will collect the follow-up data for three years to assess the durability of treatment response, hence needs to be done post-approval.

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.”

An interim study report from the ongoing trial GS-US-248-0122, entitled, “A Long Term Follow-up Registry for Subjects Who Achieve a Sustained Virologic Response to Treatment in Gilead-Sponsored Trials in Subjects with Chronic Hepatitis C Infection”, with the three year follow-up data from: GS-US-337-0102 (ION-1), GS-US-337-0109 (ION-2), GS-US-337-0108 (ION-3) will provide long-term data on the durability of treatment response.

The primary objective of this registry is to assess the durability of sustained virologic response (SVR) following treatment in a Gilead-sponsored trial. The secondary objectives of this registry are to determine whether subsequent detection of HCV RNA in subjects who relapse following SVR, represents the re-emergence of pre-existing virus, the development of resistance mutations, or whether it is due to re-infection; to assess clinical progression of liver disease; and to screen for the development of hepatocellular carcinoma (HCC). Once enrolled, subjects will be followed for up to 3 years. Visits will occur at Baseline and then at Weeks 24, 48, 72, 96, 120 and 144. At each visit, subjects will have blood drawn for plasma HCV RNA quantification, liver function tests, platelets, coagulation test, α -fetoprotein, and a quality of life survey will be completed. If HCV RNA is detected, the subject will have a repeat blood sample drawn for confirmation. If HCV RNA is confirmed the subject will be withdrawn from the Registry. If the confirmed HCV RNA is > 1000 IU/ml, viral sequence analysis will be performed.

The listed three trials are the Phase 3 registrational trials supporting dosing and administration recommendations.

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.

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

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)

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

/s/

LINDA C ONAGA
09/26/2014

WILLIAM B TAUBER
09/26/2014

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 # NDA 205834
Product Name: Ledipasvir/sofosbuvir fixed dose combination tablet

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

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>0714/2014</u>
	Study/Trial Completion:	<u>6/30/2018</u>
	Final Report Submission:	<u>2/28/2019</u>
	Other: _____	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/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

Adult studies are completed and ready for approval. The review team met with the Pediatric Review Committee (PeRC) on August 6, 2014. The PeRC agreed with the Division to grant a deferral for pediatric patients aged 3 through 17 years because the product is ready for approval in adults.

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 study is a deferred pediatric trial under PREA to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of ledipasvir/sofosbuvir for the treatment of chronic hepatitis C virus (HCV) infection in pediatric subjects 3 through 17 years of age. The Division is in general agreement with the Applicant's overall pediatric plan.

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.

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

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)

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 # NDA 205834
Product Name: Ledipasvir/sofosbuvir fixed dose combination tablet

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

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>05/2014</u>
	Study/Trial Completion:	<u>2/28/2023</u>
	Final Report Submission:	<u>8/31/2023</u>
	Other:	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/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

Adult studies are completed and ready for approval. This PMR will provide long-term safety data in pediatric subjects treated in the ledipasvir/sofosbuvir safety, pharmacokinetic and efficacy study.

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 study is a deferred pediatric study under PREA for the treatment of chronic hepatitis C virus (HCV) infection in pediatric subjects 3 through 17 years of age. The study will collect and analyze long-term safety data for subjects enrolled in the pediatric ledipasvir/sofosbuvir safety, pharmacokinetic and efficacy study. Data collected should include at least 3 years of follow-up in order to characterize the long-term safety of ledipasvir/sofosbuvir including growth assessment, sexual maturation and characterization of ledipasvir/sofosbuvir resistance associated substitutions in viral isolates from subjects failing therapy.

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.

Pediatric subjects 3 through 17 years of age with chronic hepatitis C. Long-term safety data for subjects enrolled in the pediatric ledipasvir/sofosbuvir safety, pharmacokinetic and efficacy study should include at least 3 years of follow-up in order to characterize the long-term safety of ledipasvir/sofosbuvir including growth assessment, sexual maturation and characterization of ledipasvir/sofosbuvir resistance associated substitutions in viral isolates from subjects failing therapy.

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)

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 # NDA 205834
Product Name: Ledipasvir/sofosbuvir fixed dose combination tablet

PMR/PMC Description: Ledipasvir 2-year rat carcinogenicity study

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>Completed</u>
	Study/Trial Completion:	<u>Completed</u>
	Final Report Submission:	<u>12/31/2015</u>
	Other: _____	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/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

The applicant should submit the final report for the ledipasvir 2-year carcinogenicity study in rats.

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.”

Ledipasvir will be administered for up to 24 weeks in certain HCV populations. Therefore, carcinogenicity studies are required and should be submitted to the NDA.

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.

2 year carcinogenicity study in rats

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)

☐ Pharmacoeconomic 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)

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 # NDA 205834
Product Name: Ledipasvir/sofosbuvir fixed dose combination tablet

PMR/PMC Description: Ledipasvir mouse carcinogenicity study

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>Completed</u>
	Study/Trial Completion:	<u>N/A</u>
	Final Report Submission:	<u>01/31/2015</u>
	Other: _____	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/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

The applicant should submit the final report for the ledipasvir 26-week carcinogenicity study in rasH2 mice.

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.”

Ledipasvir will be administered for up to 24 weeks in certain HCV populations. Therefore, carcinogenicity studies are required and should be submitted to the NDA.

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.

carcinogenicity study in mice

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)

☐ Pharmacoeconomic 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)

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 # NDA 205834
Product Name: Ledipasvir/sofosbuvir fixed dose combination tablet

PMR/PMC Description: Submit longitudinal data on persistence of NS5A resistance substitutions from subjects who did not achieve SVR12 in Phase 2 studies of LDV with other DAAs.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	6/21/2012
	Study/Trial Completion:	N/A
	Final Report Submission:	3/31/2015
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/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

Treatment emergent NS5A resistance substitutions were detected in many subjects who failed LDV treatment. Data from subjects who failed on other NS5A inhibitors showed that NS5A resistance substitutions have been found to persist at least a year or longer after failure on treatment. No data has been submitted on the persistence of ledipasvir or sofosbuvir resistant-associated substitution from treatment failures. It is important to understand approximately how long the NS5A resistance substitutions persist in subjects who fail treatment on a LDV regimen.

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.”

Treatment emergent NS5A resistance-associated substitutions may confer cross-resistance with other NS5A inhibitors and affect future treatment options with NS5A inhibitors. Since the presence of NS5A resistance-associated substitutions may affect future treatment options with other NS5A inhibitors, we want to understand how long these substitutions persist.

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)

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 # NDA 205834
Product Name: Ledipasvir/sofosbuvir fixed dose combination tablet

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

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>N/A</u>
	Study/Trial Completion:	<u>N/A</u>
	Final Report Submission:	<u>03/31/2015</u>
	Other: _____	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/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

Treatment emergent substitution at highly conserved amino acid positions 112, 237, and 473 of the NS5B polymerase appeared to be associated with treatment failure in two or more subjects. Understanding the susceptibility of sofosbuvir to HCV GT1a with substitutions at these positions will be important for defining potential resistance pathways and/or identifying cross-resistance to other drugs in this class.

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.”

There is the potential for treatment failure, development of resistance to ledipasvir, and/or cross-resistance to other drugs in the class if HCV GT1a with substitutions at highly conserved positions amino acid 112, 237, and 473 are less susceptible to sofosbuvir. The goal of this PMR is to determine if these substitutions have an impact on sofosbuvir susceptibility.

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)

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 # NDA 205834
Product Name: Ledipasvir/sofosbuvir fixed dose combination tablet

PMR/PMC Description: Submit the final report and datasets for the ongoing trial GS-US-337-0123, entitled “A Phase 2, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/Ledipasvir Fixed-Dose Combination + Ribavirin Administered in Subjects Infected with Chronic HCV who have Advanced Liver Disease or are Post-Liver Transplant”, in order to provide safety data and dosing recommendations for subjects with decompensated cirrhosis and/or in subjects receiving concomitant immunosuppressive agents post-liver transplant (e.g., cyclosporine).

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>08/07/2013</u>
	Study/Trial Completion:	<u>03/31/2015</u>
	Final Report Submission:	<u>09/30/2015</u>
	Other:	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/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

The Applicant initiated the trial GS-US-337-0123 entitled, “A Phase 2, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/Ledipasvir Fixed-Dose Combination + Ribavirin Administered in Subjects Infected with Chronic HCV who have Advanced Liver Disease or are Post-Liver Transplant”, prior to submission of the NDA.

Data obtained from GS-US-337-0123 will 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. 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 safety and efficacy of ledipasvir/sofosbuvir have not been established in patients with decompensated cirrhosis and/or in patients receiving concomitant immunosuppressive agents post-liver transplant (e.g., cyclosporine), thus this PMR is designed to obtain safety data and dosing recommendations in these populations.

The largest known magnitude of a drug interaction effect on sofosbuvir is caused by cyclosporine (sofosbuvir AUC ↑353%, C_{max} ↑154%), but is not deemed clinically significant as noted in the SOVALDI prescribing information. Ledipasvir causes about a 2.5-fold increase in sofosbuvir exposure. Therefore, higher sofosbuvir exposures may be achieved in the context of ledipasvir/sofosbuvir and cyclosporine coadministration. In GS-US-334-0126 in post-transplant subjects receiving sofosbuvir+ribavirin, sofosbuvir exposure data are available for 9 out of 10 HCV-infected subjects who received a cyclosporine-containing immunosuppressive regimen and 26 out of 30 subjects who did not receive cyclosporine as part of their immunosuppressive regimen. For sofosbuvir, specifically, exposures (AUC_{tau} and C_{max}) were slightly increased approximately 15% and 4%, respectively, in subjects on cyclosporine-containing regimens compared with those on a non-cyclosporine-containing regimen. In contrast to the results from the phase 1 drug-drug interaction trial (P7977-1819) where a 4.5-fold increase in sofosbuvir exposure was observed with a single dose of cyclosporine 600 mg, pharmacokinetic data from GS-US-334-0126 demonstrate that administration of clinically relevant doses of cyclosporine (75 mg to 225 mg) are not associated with substantial increases in sofosbuvir. Therefore, sofosbuvir in the context of ledipasvir/sofosbuvir may be coadministered with cyclosporine without dose adjustment.

GS-US-337-0123 entitled, “A Phase 2, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/Ledipasvir Fixed-Dose Combination + Ribavirin Administered in Subjects Infected with Chronic HCV who have Advanced Liver Disease or are Post-Liver Transplant”, is designed to evaluate the safety and efficacy of ledipasvir/sofosbuvir plus ribavirin for 12 or 24 weeks in subjects with chronic HCV genotype 1 or 4 infection with advanced liver disease or who are post-liver transplant, including those with decompensated cirrhosis. This decompensated liver disease/post-transplant population has known associated comorbidities and is overall a sicker population compared with the population enrolled in the phase 3 ledipasvir/sofosbuvir trials. The Safety Update Report submitted with this NDA included preliminary safety data from 307 subjects enrolled in GS-US-337-0123. Overall there was no clustering of events and the increased incidence of serious adverse events and deaths (eight reported deaths) did not raise concern at the time of the Clinical NDA Review. The data were used to support labeling recommendations in patients with severe hepatic impairment.

The GS-US-337-0123 final study report and datasets are identified as a PMR in order to obtain additional safety data and provide dosing recommendations for patients with decompensated cirrhosis and/or in patients receiving concomitant immunosuppressive agents post-liver transplant (e.g., cyclosporine). The Applicant is collecting samples for pharmacokinetic analysis for ledipasvir and sofosbuvir exposures in GS-US-337-0123. These data will provide additional insight into the mechanism of higher sofosbuvir exposures in the setting of ledipasvir/sofosbuvir and cyclosporine coadministration.

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.

Submit the final report and datasets for the ongoing trial GS-US-337-0123, entitled “A Phase 2, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/Ledipasvir Fixed-Dose Combination + Ribavirin Administered in Subjects Infected with Chronic HCV who have Advanced Liver Disease or are Post-Liver Transplant”, in order to provide safety data and dosing recommendations for subjects with decompensated cirrhosis and/or in subjects receiving concomitant immunosuppressive agents post-liver transplant (e.g., cyclosporine).

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)

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 # NDA 205834
Product Name: Ledipasvir/sofosbuvir fixed dose combination tablet

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

PMR/PMC Schedule Milestones:	Final Protocol Submission:	12/02/2013
	Study/Trial Completion:	03/15/2016
	Final Report Submission:	08/16/2016
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/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

GS-US-337-0115, entitled “A Phase 3, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination for 12 Weeks in Subjects with Chronic Genotype 1 or 4 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV)-1 Co-infection”, was an ongoing trial during review of the NDA.

Data obtained from GS-US-337-0115 will provide safety data in subjects receiving concomitant ledipasvir/sofosbuvir and Atripla (or its components) and will provide dosing recommendations for HCV/HIV-1 co-infected patients.

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.”

Obtain safety data in subjects receiving concomitant ledipasvir/sofosbuvir and Atripla (or its components) and obtain dosing recommendations for HCV/HIV-1 co-infected patients.

The phase 1 trial, GS-US-337-0127, entitled, “A Phase 1 Study to Evaluate Pharmacokinetic Drug-Drug Interactions between Sofosbuvir/Ledipasvir (SOF/LDV) Fixed-Dose Combination (FDC) Tablet and Antiretroviral Regimens Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate (EFV/FTC/TDF; Atripla®) or Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate (FTC/RPV/TDF; Complera®), and the Relative Bioavailability and Pharmacokinetics of SOF/LDV FDC upon Administration with a Representative H2-Receptor Antagonist or a Proton Pump Inhibitor”, demonstrated ledipasvir/sofosbuvir and efavirenz/emtricitabine/tenofovir (Atripla) coadministration increases tenofovir AUC, Cmax and Ctau by 98%, 79% and 163%, respectively. The magnitude of the increase in tenofovir exposures is higher compared to other drug interaction trials with tenofovir and the concern with ledipasvir/sofosbuvir and Atripla coadministration is for tenofovir-associated toxicities, specifically renal events.

GS-US-337-0115, entitled “A Phase 3, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination for 12 Weeks in Subjects with Chronic Genotype 1 or 4 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV)-1 Co-infection”, is an ongoing trial designed to enroll approximately 300 subjects with HCV/HIV-1 co-infection.

The GS-US-337-0115 final study report and datasets are identified as a PMR in order to provide safety data in subjects receiving concomitant ledipasvir/sofosbuvir and Atripla (or its components) and to provide dosing recommendations for HCV/HIV-1 co-infected patients.

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.

This trial is a phase 3 trial in HCV/HIV-1 co-infected subjects

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/

LINDA C ONAGA
09/22/2014

WILLIAM B TAUBER
09/22/2014

**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: August 26, 2014

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: Karen Dowdy, RN, BSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Kemi Asante, Pharm.D.
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

Applicant: Gilead Sciences, Inc.

1 INTRODUCTION

On February 8, 2014, Gilead Sciences, Inc. submitted for the Agency's review New Drug Application (NDA) 205834 for HARVONI (ledipasvir and sofosbuvir) tablets with the proposed indication for the treatment of chronic genotype 1 hepatitis C virus (HCV) 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 the requests by the Division of Antiviral Products (DAVP) on February 19, 2014 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for HARVONI (ledipasvir and sofosbuvir) tablets.

2 MATERIAL REVIEWED

- Draft HARVONI (ledipasvir and sofosbuvir) tablets PPI submitted on February 8, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 13, 2014.
- Draft HARVONI (ledipasvir and sofosbuvir) tablets Prescribing Information (PI) submitted on February 8, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 13, 2014.
- Approved SOVALDI (sofosbuvir) tablets comparator labeling dated December 6, 2013.

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.

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)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

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.

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/s/

KAREN M DOWDY
08/26/2014

OLUWASEUN A ASANTE
08/26/2014

BARBARA A FULLER
08/26/2014

LASHAWN M GRIFFITHS
08/26/2014

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

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

Memorandum

Date: August 26, 2014

To: Linda Onaga
Regulatory Project Manager
Division of Antiviral Products (DAVP)

From: Kemi Asante, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 205834
Harvoni™ (ledipasvir and sofosbuvir) tablets, for oral use

In response to DAVP's February 19, 2014 consult request, OPDP has reviewed the proposed package insert (PI), patient package insert (PPI) and carton/container labeling for Harvoni™ (ledipasvir and sofosbuvir) tablets, for oral use.

Comments on the PI are provided below and are based on the version of the PI accessed from the following link provided by DAVP via email on August 13, 2014: <http://sharepoint.fda.gov/orgs/CDER-OAP-DAVP/davpactiveprojecsts/Shared%20Documents/Onaga,%20Linda/LDV%20SOF%20Labeling.docx>.

Please note that comments on the PPI will be provided under separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP). We have no comments on the draft carton/container labeling accessed from the following EDR location on August 26, 2014, \\CDSESUB1\evsprod\NDA205834\205834.enx

OPDP appreciates the opportunity to provide comments. If you have any questions, please contact me at 301-796-7425 or Kemi.Asante@fda.hhs.gov.

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/s/

OLUWASEUN A ASANTE
08/26/2014

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum: August 21, 2014
Requesting Office or Division: Division of Antiviral Products (DAVP)
Application Type and Number: NDA 205834
Product Name and Strength: Harvoni (ledipasvir/sofosbuvir) Tablets, 90 mg/400 mg
Submission Date: August 14, 2014
Applicant/Sponsor Name: Gilead Sciences, Inc.
OSE RCM #: 2014-353-1
DMEPA Primary Reviewer: Mónica Calderón, PharmD, BCPS
DMEPA Team Leader: Irene Chan, PharmD, BCPS

1 PURPOSE OF MEMO

Division of Antiviral Products requested that we review the revised container labels and Full Prescribing Information (FPI) (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSIONS

The revised container labels and FPI are acceptable from a medication error perspective.

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¹ Calderon M. Label and Labeling Review for Harvoni (NDA 205834). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 Jul 1. 32 p. OSE RCM No.: 2014-353.

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/s/

MONICA M CALDERON
08/21/2014

IRENE Z CHAN
08/22/2014

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:	July10, 2014
Requesting Office or Division:	Division of Antiviral Products (DAVP)
Application Type and Number:	NDA 205834
Product Name and Strength:	Harvoni (ledipasvir/sofosbuvir) Tablets, 90 mg/400 mg
Product Type:	Multi-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Gilead Sciences, Inc.
Submission Date:	February 8, 2014
OSE RCM #:	2014-353
DMEPA Primary Reviewer:	Mónica Calderón, PharmD, BCPS
Associate Director:	Irene Chan, PharmD, BCPS

1 REASON FOR REVIEW

Gilead Sciences submitted this application, NDA 205834, for the treatment of chronic hepatitis C (CHC) genotype 1 infection. Thus, the Division of Antiviral Products (DAVP) requested DMEPA evaluate the Applicant's proposed container label and full prescribing information (FPI) for areas of vulnerability that could lead to medication errors. The Applicant also submitted carton labeling and container labels for the Gilead Access Program with this submission.

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.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B (N/A)
Previous DMEPA Reviews	C (N/A)
Human Factors Study	D (N/A)
ISMP Newsletters	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant is proposing a single strength (90 mg /400 mg), dual-ingredient tablet. The product will be packaged in a 28-count bottle, which is supported by the dosage and administration of this product. DMEPA performed a risk assessment of the proposed commercial container label and FPI and determined that important information is displayed clearly on the label and the Dosage and Administration section is clearly stated within the FPI. Our review of the carton labeling and container labels for the Gilead Access Program determined that the labels and labeling are identical to the commercial products with the exception of the added statement (b) (4). Our only recommendation is that all labels and labeling should be updated to reflect the conditionally acceptable proprietary name, Harvoni.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes the labels and labeling are acceptable from a medication error perspective. We only recommend that the “TRADENAME” statement be replaced with the conditionally acceptable proprietary name, Harvoni, where applicable throughout the labels and labeling.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Harvoni that Gilead Sciences, Inc. submitted on February 8, 2014.

Table 2. Relevant Product Information for Harvoni	
Active Ingredient	ledipasvir/sofosbuvir
Indication	Treatment of chronic hepatitis C genotype 1 infection
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	Store at room temperature below 30 °C (86 °F).

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/s/

MONICA M CALDERON
07/10/2014

IRENE Z CHAN
07/11/2014

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: June 20, 2014

TO: Linda Onaga, Regulatory Health Project Manager
Sarah Connelly, M.D. Medical Officer
Division of Antiviral Products

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

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

Kassa Ayalew, M.D., MPH
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 205-834

APPLICANT: Gilead Sciences Inc.

DRUG: ledipasvir/sofosbuvir fixed dose combination tablets

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority review
INDICATION: Treatment of chronic HCV-infected adults
CONSULTATION REQUEST DATE: February 28, 2014
DIVISION ACTION GOAL DATE: October 10, 2014
PDUFA DATE: October 10, 2014
INSPECTION SUMMARY DUE DATE: August 11, 2014

I. BACKGROUND:

The Applicant conducted three pivotal trials in support of approval of Ledipasvir a new molecular entity for the treatment of chronic genotype-1 HCV infection in adult patients.

The pivotal clinical Protocols GS-US-337-0102, GS-US-337-0108 and GS-US-337-0109 were conducted to support the pending application.

Protocols: GS-US-337-0102 entitled “A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/GS-5885 Fixed-Dose Combination+ Ribavirin for 12 and 24 Weeks in Treatment-Naïve Patients With Chronic Genotype 1 Chronic Hepatitis C (HCV) Infection”,

GS-US-337-0108 entitled “A Phase 3, Multicenter, Randomized, Open-Label Study To Investigate the Safety and Efficacy of Sofosbuvir/Ledipasvir Fixed-Dose Combination+ Ribavirin for 8 and Sofosbuvir/Ledipasvir Fixed Combination for 12 Weeks in Treatment-Naïve Patients With Chronic Genotype 1 Chronic Hepatitis C (HCV) Infection”, and

GS-US-337-0109 entitled “A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/GS-5885 Fixed-Dose Combination+ Ribavirin for 12 and 24 Weeks in Treatment-Experienced Patients With Chronic Genotype 1 Chronic Hepatitis C (HCV) Infection”.

The review division requested inspection of six clinical investigators for the pivotal studies noted above because data from the studies are considered essential to the approval process. These sites were targeted for inspection due to 1) enrollment of a relatively large number of subjects with a treatment effect that was greater than average, 2) large number of discontinuations, significant primary efficacy results pertinent to decision-making , and 3) the need to determine if sites conducted the trial ethically and were in compliance with GCP regulations.

II. RESULTS (by protocol/site):

Name of CI, Location, and Site #	Protocol and # of subjects screened & randomized	Inspection Dates	Final Classification
Mario Chojkier, M.D. 3350 La Jolla Village Dr. Dr.111-d San Diego, CA 92161 Site #4435	Protocol GS-US-337-0102 Number of subjects: 21/17	4/9-24/2014	Pending (preliminary classification VAI)
Norman Gitlin, M.D. 550 Peachtree North St. Atlanta, GA 30308 Site #2111	Protocol GS-US-337-0102 Number of subjects: 18/17	4/14-18/2014	Pending (preliminary classification NAI)
Ronald, Pruitt, M.D. 4230 Harding Rd. Nashville ,TN 37205 Site #5847	Protocol GS-US-337-0108 Number of subjects: 23/17	4/2-11/2014	Pending (Preliminary classification VAI)
Adrian DiBisceglie, M.D. 3545 Lafayette Ave. 2nd Floor Saint Louis, MO 63104 Site #0334	Protocol GS-US-337-0108 Number of subjects: 29/25	4/2-9/2014	Pending (preliminary classification VAI)
Nezam Afdhal, M.D 110 Francis Street, Suite 4A Boston, MA 02215 Site #0519	Protocol GS-US-337-0109 Number of subjects: 20/17	4/7-16/2014	Pending (preliminary classification NAI)
David Nelson, M.D. 2004Mowry Road, Rm. 2258 Gainesville, FL 32610 Site# 4232	Protocol GS-US-337-0109 Number of Subjects 18/17	4/22-24/2014	Pending (preliminary classification NAI)

Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations. Data 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. Mario Chojkier, M.D
San Diego, CA 92161

- a. What Was Inspected:** This inspection was performed as a data audit for NDA 205-834 and inspected Study Protocol GS-US-337-0102. At this site, a total of 21 subjects were screened, two subjects were reported as screen failures, 19 subjects were randomized into the study, and all 19 subjects completed the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

The medical records/source data for nine subjects were reviewed and compared to data listings. The review included drug accountability records, 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.

- b. General Observations/Commentary:** At the conclusion of the inspection, a Form FDA 483 was issued to Dr. Chojkier because of minor protocol deviations such as non-reporting of adverse events and concomitant medications. For example,

Subject #4435-71138 was treated for gout from 4/20/13 to 5/1/13; however this was not reported to the sponsor.

Subjects #4435-71138 at Week 24 and Subject# 4435-71731 at week 10 both received prednisone and ibuprofen respectively for headache; however these medications were not reported in their respective case report forms.

Subjects 4435-71138's and 4435-71381's Week 1 source documents recorded ECGs as "abnormal-not clinical significant"; however, the ECGs were reported as "normal" in their respective electronic case report form. In addition, one subject was out-of-window for 3 separate visits. Inadequate record keeping was discussed with the clinical investigator at the close of the inspection.

The clinical investigator acknowledged the inspectional findings in a letter dated May 14, 2014 in which he agreed with inspectional findings and provided adequate explanations to include implementation of corrective actions to prevent the recurrence of the inspectional findings. OSI finds his response acceptable/adequate.

In general, the medical records reviewed were found to be organized, and the data verifiable except for the primary efficacy endpoint due to the double-blind nature of the serum HCV RNA results for all post treatment visits. There were no deaths reported at this site. There were no known limitations to the inspection. The study appears to have been conducted adequately, and the data generated may be used to support the pending application.

- c. Assessment of Data Integrity:** The minor deviations noted at this site are not expected to impact the outcome of the study. The data generated in support of the

clinical efficacy and safety at Dr. Chojkier's site are considered reliable and acceptable in support of the pending application.

2. Normal Gitlin, M.D.
Atlanta, GA 30308

- a. What Was Inspected:** This inspection was performed as a data audit for NDA 205-834 and inspected study Protocol GS-US-337-0102. At this site, a total of 18 subjects were screened, one subject was reported as a screen failure, and 17 subjects were randomized into the study and all subjects completed the study. Review of the Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed informed consent forms prior to enrollment.

The medical records/source documents for eight subjects were reviewed. The medical records/source documents for enrolled subjects for certain visits were reviewed including drug accountability records, vital signs, IRB files, inclusion/exclusion criteria, prior and concomitant medications, and adverse events reporting. The field investigator compared the source documents/endpoint values to the data listings for primary efficacy endpoints, and no discrepancies were noted.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Gitlin. The medical records reviewed were found to be in order 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.
- c. Assessment of Data Integrity:** The data in support of the clinical efficacy and safety at Dr. Gitlin's site are considered reliable and may be used in support of the pending application.

3. Ronald Pruitt, M.D.
Nashville, TN37205

- a. What Was Inspected:** This inspection was performed as a data audit Protocol GS-US-337-0108. At this site, a total of 23 subjects were screened, three subjects were reported as screen failures, twenty (20) subjects were randomized into the study, and 17 subjects completed the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

The medical records/source data for all subjects were reviewed including drug accountability records, vital signs, IRB records, 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 listing.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Pruitt. However, our investigation found that the informed consent document did not include an explanation of whom to contact in the event of research related injury to the subject.

There was no evidence of under-reporting of adverse events at this site. However, for one subject who experienced one event of chest pain was not reported to the sponsor. In addition, minor discrepancies existed between source documents and what was reported in the case report forms for 8 of 20 subjects regarding the use of concomitant medications and ECGs. These minor errors were discussed with the clinical investigator.

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 with exception noted above.

- c. Assessment of Data Integrity:** Although minor regulatory deviations were noted, the findings are unlikely to affect integrity of the data as it appears to be an isolated incidence and not systemic in nature. The data from Dr. Pruitt's site are considered reliable and appear acceptable in support of the pending application.

**4. Adrian DiBisceglie, M.D.
Saint Louis, MO 63104**

- a. What Was Inspected:** This inspection was performed as a data audit Study Protocol GS-US-337-0108. At this site, a total of 29 subjects were screened, four subjects were reported as screen failures, 25 subjects were randomized into the study, and 23 subjects completed the study. Two subjects were reported as lost to-follow-up. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

The medical records/source data for 13 subjects were reviewed and compared to data listings. The review included consent forms, drug accountability records, inclusion/exclusion criteria, vital signs, IRB records, sponsor correspondence, primary and secondary efficacy endpoints and adverse events. In addition, a cursory review included the inclusion/exclusion criteria, adverse events and secondary outcomes for the remaining enrolled subjects. Source documents were compared to case report forms and data listings including for primary efficacy endpoints and adverse events listings.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. DiBisceglie. The medical records reviewed were found to be in order, organized, and the data verifiable; however, our investigator found an adverse event of rectal pain reported in the case report form as attributable to the study drug which was changed in the source document to not attributable. In addition, our investigator noted that one subject was screened on 5/6/13 and was enrolled on 6/17/13 who was in rehab for narcotics addiction for 30 days in (b) (6). The "site

was informed that the subject had not used drugs but went to rehab because he felt he was going to use”. As a result, the subject was prescribed Suboxone, a prohibited medication throughout the study. It appears that there was a potential narcotics abuse within a year of screening which met exclusionary criterion and the subject should have been excluded from enrollment. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection. The study appears to have been conducted adequately, and the data generated may be used to support the pending application.

- c. **Assessment of Data Integrity:** With the exception of the deviations noted above, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the pending application.

5. Nezam Afdhal, M.D.
Boston, MA 02215

- a. **What was Inspected:** This inspection was performed as a data audit for NDA 205-834 and inspected study GS-US-337-0109. At this site, a total of 20 subjects were screened, three subjects were reported as screen failures, 17 subjects were randomized into the study, and 17 subjects completed the study. Review of the Informed Consent Documents for all subjects verified that all subjects signed informed consent forms prior to enrollment.

The medical records/source documents for all subjects were reviewed for primary/secondary endpoints. The medical records for the majority of subjects were reviewed in depth, including drug accountability records, vital signs, IRB files, inclusion/exclusion criteria, study procedures, monitoring procedures, and use of concomitant medications. Source documents were compared to CRFs and data listings, to include primary efficacy endpoints and adverse events.

- c. **General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Afdhal. However, minor protocol deviations were discussed with clinical investigator which included the failure to reduce the dose of ribavirin in accordance with the protocol. The protocol calls for a hemoglobin lower than 10 mg/dL to have their dose reduced to 600 mg/day. The clinical investigator reduced the dose to 800 mg/dL instead of 600 mg/dL with a hemoglobin level of 9.9 mg/dL. The other discussion point dealt with the classification of non-responder subjects. At times there was no viral load results during the first 12 weeks of previous treatment, the clinical investigator stated that from the subjects’ history he was confident that the subject was non-responder.

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.

- d. **Assessment of Data Integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the pending application.

**6. David Nelson M.D.
Gainesville, FL 32610**

- a. **What was Inspected:** This inspection was performed as a data audit for study GS-US-337-0109. At this site, a total 18 subjects were screened, one subject was reported as a screen failure, 17 subjects were randomized into the study, and 17 subjects completed the study. Review of the Informed Consent Documents for all subjects verified that all subjects signed informed consent forms prior to enrollment.

The medical records/source documents for 10 subjects were reviewed. A review of seven subjects including informed consent, adverse events, concomitant medications, primary efficacy endpoint, and basic inclusion/exclusion criteria was made. The medical records for the majority of subjects were reviewed in depth, including drug accountability records, vital signs, IRB files, inclusion/exclusion criteria, study procedures, monitoring procedures, and use of concomitant medications. Source documents were compared to CRFs and data listings, to include primary efficacy endpoints and adverse events.

- b. **General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Nelson. However, our investigator discussed with the clinical investigator the discrepant records regarding the response to prior treatment for one subject and the stop date for a prohibited concomitant medications for two subjects. 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.
- c. **Assessment of Data Integrity:** With the exception of the discussion points noted above, the data generated in support of the clinical efficacy and safety at Dr. Nelson's site are considered reliable and acceptable in support of the pending application.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Six clinical investigator sites were inspected in support of this application. The inspection of the six clinical investigators listed above revealed minor or no regulatory violations. The pending classification for Drs. Chojkier, Pruitt and DiBisceglie sites are Voluntary Action Indicated (VAI) and the pending classification for the other three Drs. Gitlin, Nelson and Afdhal sites are No Action Indicated (NAI). An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR. Overall, the data submitted from these six sites are considered acceptable in support of the pending application.

{See appended electronic signature page}

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

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
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Kassa Ayalew, M.D. M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

ANTOINE N EL HAGE
06/23/2014

SUSAN D THOMPSON
06/23/2014

KASSA AYALEW
06/23/2014

Division of Hematology Products
Office of Hematology Oncology Drug Products, CDER
Consultation Reply

Date: May 13, 2014

TO: Sarah Connelly, MD
Kendall Marcus, MD; DDS
Division of Anti-Viral Drug Products, CDER

RE: IND 106739
NDA 204671
Sofosbuvir 400 mg tablets

Development of Factor 8 inhibitor associated with Sofosbuvir or Ledipasvir/
Sofosbuvir combination therapy of hepatitis C

FROM: Robert Kane, MD, DDS, Division of Hematology Products (DHP)

Reason for Consult:

Due to the reports of two cases of appearance of Factor VIII inhibitors in trials of anti-viral therapy of HCV, one case after Sofosbuvir alone and one after the combination of Sofosbuvir and ledipasvir, DAVP requests this consult to:

- (1) Obtain your causality assessment between development of Factor VIII inhibitors and use of sofosbuvir and/or ledipasvir/sofosbuvir-containing regimens.
- (2) Determine if labeling is recommended for risk communication of these events.
- (3) Determine if any postmarketing commitments/requirements are recommended to address this safety issue.
- (4) Any additional monitoring, labeling or postmarketing recommendations based on your assessment of these reported cases.

Consult Reply:

(1) Obtain your causality assessment between development of Factor VIII inhibitors and use of sofosbuvir and/or ledipasvir/sofosbuvir-containing regimens.

The development of Factor VIII inhibitors is unlikely to be related to the drug Sofosbuvir or the combination of ledipasvir/sofosbuvir. Patients with hemophilia have a high prevalence of hepatitis C for various reasons including prior blood product exposure and may develop inhibitors (antibodies) to factor 8 periodically during their life, sometimes related to their receipt of various factor 8 containing products as factor 8 replacement therapy. The inhibitors are antibodies (primarily IgG) directed against the specific deficient factor and generally associated with more severe factor deficiencies (and more use of replacement therapy). The two reported cases encountered thus far in the trials are heavily confounded, and a preliminary look by the sponsor does not indicate other cases. The cases most likely are coincidental and related to factor 8 product infusion or variable natural history of hemophilia. Further evidence is pending for case 71745. Factor 8 Inhibitors may appear in up to 25% of hemophilia A patients, especially those with more severe deficiency, and perhaps 5% of patients with milder hemophilia. Thus,

the appearance of an inhibitor among hemophilia patients can be expected with some frequency by chance in the sofosbuvir trials. In some hemophilia patients, inhibitors can reoccur a number of times, most often following factor 8 replacement therapies. A U.K. study reported the incidence of "new" inhibitors of 5/1000 patient years in the "severe" hemophilia population aged 10-60 years.¹

The evidence to date of the two cases in the trial data does not support a causality inference.

The host factors that enhance the risk of development of inhibitors are not known, and there are many molecular types of hemophilia. The sponsor should continue to monitor pro-actively for the possibility of a relationship of factor 8 inhibitor development to the drug therapy in hemophilia patients, since it is theoretically possible that the interaction of the viral infection (HCV), the chronic liver disease, the hemophilia, the periodic use of plasma-derived or recombinant factor infusions, and the anti-viral drugs could alter patients' immunity in novel ways. The sponsor should consider evaluating the hemophilia patients as a separate subset, to include documentation of more details of their prior history, their use of replacement therapies (name of specific products used, dates of administration and total doses in the recent past (12 months) prior to study entry and for 12 months after end of anti-viral therapy, etc.

(2) Determine if labeling is recommended for risk communication of these events.

No change in labeling is indicated based on this data of the 2 cases to date.

(3) Determine if any postmarketing commitments/requirements are recommended to address this safety issue.

No. However, the sponsor should monitor for this event as an event of special interest to obtain more data prospectively in current trials. Monitoring can be by interim history alone. Spontaneous bleeding or the detection of a markedly prolonged aPTT (longer than usual for that patient) are signs of development of an inhibitor in a patient who is otherwise stable. No additional on-study labs should be required, although the sponsor may choose to add labs.

(4) Any additional monitoring, labeling or postmarketing recommendations based on your assessment of these reported cases.

The sponsor should amend current trials to require determination of a positive or negative history of factor 8 inhibitor in hemophilia patients being screened for the trials (not as an exclusion criterion, only as data) and should test a cohort of hemophilia A patients at baseline for the presence of a factor 8 inhibitor, in sufficient numbers to be able to assess the incidence of treatment-emergent appearance of an inhibitor in their therapy program (during therapy and for 12 months after completion of anti-viral Rx. Again, the presence of an inhibitor is not intended to be an exclusion criterion for trials, only to establish baseline prevalence. The

¹ Incidence of factor VIII inhibitors throughout life in severe hemophilia A in the United Kingdom. Hay CR, Palmer B, Chalmers E, Liesner R, Maclean R, Rangarajan S, Williams M, Collins PW, United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) Blood. 2011;117(23):6367

sponsor should again be requested to send in the full hematology consult on patient 1675, as previously requested.

Please re-consult us if we can be of further assistance.

Background:

Two cases of Factor VIII inhibition have been reported to FDA in hepatitis C subjects with hemophilia, one treated with sofosbuvir SOF plus ribavirin, and one treated with ledipasvir/sofosbuvir (LDV/SOF)-containing regimens.

- Subject 1675, case #2014-0094263, (SOF+RBV therapy; IND 106739, SN0428, 17 April 2014), a 47 y/o male, received daily high-dose Factor VIII replacement during surgery for a tibia/fibula fracture on Day (b) (6) after completion of SOF+RBV therapy, developed intractable hemarthrosis in his elbows on Day 74, received courses of Advate, 2000U BID, and was diagnosed with an inhibitor on Day 120, high titer BU. The development of a factor VIII inhibitor occurred after approximately 4 weeks of high-dose factor VIII replacement and more than 10 weeks after completing SOF+RBV therapy.
 - Subject 71745 (LDV/SOF therapy; IND 115268, SN0146, 04 March 2014), was exposed to LDV/SOF for 5 months prior to experiencing spontaneous bleeding and found to have developed an inhibitor. Inhibitor levels fell after LDV/SOF discontinuation.
-

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/s/

LINDA C ONAGA
05/19/2014

ROBERT C KANE
05/19/2014

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 #: BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: ledipasvir/sofosbuvir Established/Proper Name: TBD Dosage Form: tablet Strengths: 90mg/400mg		
Applicant: Gilead Sciences, Inc. Agent for Applicant (if applicable):		
Date of Application: February 7, 2014 Date of Receipt: February 10, 2014 Date clock started after UN:		
PDUFA Goal Date: October 10, 2014	Action Goal Date (if different):	
Filing Date: April 11, 2014	Date of Filing Meeting: March 11, 2014	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 1/4		
Proposed indication(s)/Proposed change(s): [TRADENAME] is a fixed-dose combination of ledipasvir, a hepatitis C virus (HCV) NS5A inhibitor and sofosbuvir, a HCV nucleotide analog NS5B polymerase inhibitor and is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 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 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 <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>		
<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<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)
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<input checked="" type="checkbox"/> Fast Track Designation <input checked="" type="checkbox"/> Breakthrough Therapy Designation <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 type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <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): IND 115268, IND 106739, IND 108214

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>				
Are the proprietary, established/proper, and applicant names correct in tracking system?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, ask the document room staff to make the corrections. Also, 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, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, 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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, ask the document room staff to make the appropriate entries.</i>				
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"/>		
<i>If yes, explain in comment column.</i>				
If affected by AIP, has OC/OMPQ 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) included with	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

authorized signature?					
User Fee Status <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: <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 type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2)		YES	NO	NA	Comment
(NDAs/NDA Efficacy Supplements only)					
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"/>	<input checked="" 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"/>	<input checked="" 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)]? <i>If you answered yes to any of the above 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</i>		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Is there unexpired exclusivity on any drug product containing the 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"/>	<input checked="" 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 the active moiety for the proposed drug product, 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? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</i>	<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)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 5 years <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<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 checked="" type="checkbox"/>	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</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 checked="" 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 checked="" 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"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
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), 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)? If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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"/>	

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

Financial Disclosure	YES	NO	NA	Comment
<p>Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><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></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><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></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Electronic CTD Submission
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 RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, 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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

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 checked="" 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 checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input checked="" type="checkbox"/> Other (specify) Access Program Labels			
	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"/>		
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?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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

4

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

Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<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, and current approved Rx PI (if switch) 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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult sent to DTOP for review of eye disorder adverse events
<i>If yes, specify consult(s) and date(s) sent:</i>				
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 type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 11, 2014

BLA/NDA/Supp #: NDA 205834

PROPRIETARY NAME: ledipasvir/sofosbuvir

ESTABLISHED/PROPER NAME: TBD

DOSAGE FORM/STRENGTH: tablets, 90mg/400mg

APPLICANT: Gilead Sciences, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

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

BACKGROUND:

Gilead Sciences, Inc. submitted an original new drug application (NDA) for ledipasvir (LDV, GS-5885) and sofosbuvir (SOF, GS-7977) together as an oral fixed-dose combination (FDC) tablet (90 mg/400 mg) for the treatment of chronic genotype 1 hepatitis C virus (HCV) infection.

Ledipasvir is a HCV NS5A inhibitor that has demonstrated potent anti-HCV activity against genotype 1a and 1b HCV infection. Sofosbuvir is a novel nucleotide NS5B polymerase inhibitor that inhibits HCV RNA replication in vitro. Sofobuvir (Sovaldi®) was approved in December 2013 for use in combination with other agents for the treatment of chronic HCV infection in adults.

LDV/SOF fixed dose combination tablets was granted Fast Track designation and Breakthrough Therapy designation on July, 2, 2012 and July 22, 2013, respectively.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Linda Onaga	Y
	CPMS/TL:	Karen Winestock	Y
Cross-Discipline Team Leader (CDTL)	Kimberly Struble		Y
Clinical	Reviewer:	Sarah Connelly	Y
	TL:	Kimberly Struble	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Lisa Naeger Eric Donaldson	Y
	TL:	Julian O'Rear	Y
Clinical Pharmacology	Reviewer:	H. Jenny Zheng	Y
	TL:	Shirley Seo	Y
Biostatistics	Reviewer:	X. Karen Qi	Y
	TL:	Fraser Smith	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Christopher Ellis	Y
	TL:	Hanan Ghantous	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	George Lunn	Y
	TL:	Stephen Miller	Y

Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Steven Donald	Y
	TL:		
CMC Labeling Review	Reviewer:	N/A	
	TL:		
Facility Review/Inspection	Reviewer:	Krishna Ghosh	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:	Robert Pratt	Y
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	Tony El-Hage	N
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Product Quality - BioPharm	Sandra Suarez Sharp		Y
OSE PM	Danayal Chaudhry		N
DMEPA	Monica Calderon/Irene Chan		N
OSE/DPV	Mihaela Jason/Kelly Cao		N
Pharmacometric	Jeff Florian/Yaning Wang		N
Patient Labeling	Karen Dowdy/Barbara Fuller		Y
OPDP	Kemi Asante		N
ADRA	Dave Roeder		
ERG Contractor			

FILING MEETING DISCUSSION:

GENERAL • 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? Describe the scientific bridge (e.g., BA/BE studies):	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
• Per reviewers, are all parts in English or English translation? If no , explain:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
• Electronic Submission comments List comments: None	<input type="checkbox"/> Not Applicable
CLINICAL Comments: None	<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
• Clinical study site(s) inspections(s) needed? If no , explain:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
• Advisory Committee Meeting needed? Comments: None If no, for an NME NDA or original BLA , include the reason. For example: <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 has breakthrough therapy designation. In addition, the application did not raise significant public health questions on the role of the drug/biologic in diagnosis, cure, mitigation, treatment or prevention of a disease.

<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments: None</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
<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>CLINICAL MICROBIOLOGY</p> <p>Comments: None</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: None</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: None</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: None</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>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <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>PRODUCT QUALITY (CMC)</p>	<input type="checkbox"/> Not Applicable

<p>Comments: None</p>	<input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<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>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments: None</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments: None</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments: None</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <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><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter

APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)		<input type="checkbox"/> N/A
<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? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
<ul style="list-style-type: none"> • If so, were the late submission components all submitted within 30 days? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	None	
<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 checked="" 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 checked="" 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 checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
REGULATORY PROJECT MANAGEMENT		
Signatory Authority: Edward Cox, MD, MPH OAP Director Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): May 21, 2013 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"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<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"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at:</p> <p>http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

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

/s/

LINDA C ONAGA
03/28/2014

KAREN D WINESTOCK
03/31/2014

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

Application Type: New NDA

Name of Drug/Dosage Form: ledipasvir/sofosbuvir fixed dose combination tablet

Applicant: Gilead Sciences

Receipt Date: February 10, 2014

Goal Date: October 10, 2014

1. Regulatory History and Applicant's Main Proposals

Gilead Sciences, Inc. submitted an original new drug application (NDA) for ledipasvir (LDV, GS-5885) and sofosbuvir (SOF, GS-7977) together as an oral fixed-dose combination (FDC) tablet (90 mg/400 mg) for the treatment of genotype 1, chronic hepatitis C virus (HCV) infection.

Ledipasvir is a HCV NS5A inhibitor that has demonstrated potent anti-HCV activity against genotype 1a and 1b HCV infection. Sofosbuvir is a novel nucleotide NS5B polymerase inhibitor that inhibits HCV RNA replication in vitro. Sofobuvir (Sovaldi[®]) was approved in December 2013 for use in combination with other agents for the treatment of chronic HCV infection in adults.

LDV/SOF fixed dose combination tablets was granted Fast Track and Breakthrough Therapy designation on July, 2, 2012 and July 22, 2013, respectively.

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

Subsection 7.3 in the Table of Contents does not match the title in the Full Prescribing Information.

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 and HORIZONTAL LINES IN THE PI

- 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 (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- 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

Selected Requirements of Prescribing Information

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
• 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

Selected Requirements of Prescribing Information

- 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.

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

- N/A** 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:

- N/A** 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:

- N/A** 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

Selected Requirements of Prescribing Information

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** 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: 7.3 does not match
- 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

NO

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: Subsection 7.3 title does not match the title in the FPI

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)]”.

Selected Requirements of Prescribing Information

Comment: *The clinical microbiology review team wants subsection 12.4 Microbiology used as the cross reference instead of Clinical Pharmacology, 12.4.*

- N/A** 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:

- N/A** 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:

Selected Requirements of Prescribing Information

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 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]
- [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

- 1.1 [text]
- 1.2 [text]

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.

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

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

/s/

LINDA C ONAGA
03/26/2014

KAREN D WINESTOCK
03/27/2014