CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208341Orig1s000

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 # 208341

Product Name: EPCLUSA; sofosbuvir and velpatasvir fixed dose combination tablet

PMR/PMC Description: Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of sofosbuvir and velpatasvir in pediatric subjects 12 through less than 18 years of age with chronic hepatitis C virus infection

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	6/30/2016
	Study Completion:	3/31/2019
	Final Report Submission:	9/30/2019
	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

   Adult trials are completed and ready for approval. The review team met with the Pediatric Review Committee (PeRC) on May 11, 2016. 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."

Reference ID: 3951086

The goal of the deferred pediatric study is to evaluate the safety, efficacy (assessed as sustained virologic response), and pharmacokinetics of (b) (4) sofosbuvir and velpatasvir in children ages 12 through less than 18 years of age with chronic hepatitis C infection. (b) (4) 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.

   A clinical study is required to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of sofosbuvir and velpatasvir in pediatric subjects 12 through less than 18 years of age with chronic hepatitis C infection.

Reference ID: 3951086

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

Reference ID: 3951086

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)

Reference ID: 3951086

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 # 208341

Product Name: EPCLUSA; sofosbuvir and velpatasvir fixed dose combination tablet

PMR/PMC Description: Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of sofosbuvir and velpatasvir in pediatric subjects 3 through less than 12 years of age with chronic hepatitis C virus infection

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	6/30/2016
	Study/Trial Completion:	10/31/2020
	Final Report Submission:	4/30/2021
	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

   Adult trials are completed and ready for approval. The review team met with the Pediatric Review Committee (PeRC) on May 11, 2016. 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."

Reference ID: 3951086

The goal of the deferred pediatric study is to evaluate the safety, efficacy (assessed as sustained virologic response), and pharmacokinetics of [redacted] (b) (4) sofosbuvir and velpatasvir in children ages 3 through less than 12 years of age with chronic hepatitis C infection. [redacted] (b) (4) he 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.

   A clinical study is required to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of sofosbuvir and velpatasvir in pediatric subjects 3 through less than 12 years of age with chronic hepatitis C infection.

   Required

   - ☐ Observational pharmacoepidemiologic study
   - ☐ Registry studies

Reference ID: 3951086

☒ 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

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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.*

Reference ID: 3951086

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(signature line for BLAs)

Reference ID: 3951086

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 # 208341
Product Name: Sofosbuvir/velpatasvir (EPCLUSA™)

PMR/PMC Description: Conduct a drug interaction study to evaluate the interaction between sofosbuvir/velpatasvir and atorvastatin.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	09/30/2016
	Study/Trial Completion:	05/31/2017
	Final Report Submission:	02/28/2018
	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

   The results from the rosuvastatin study indicate that velpatasvir can significantly increase the concentration of substrates of organic anion transporting polypeptides (OATP) and breast cancer resistance protein (BCRP), such as atorvastatin. Although the results from the rosuvastatin drug interaction study cannot be directly extrapolated to atorvastatin, there is a mechanistic basis for a potentially clinically significant interaction with atorvastatin (a commonly used statin). Furthermore, a serious safety risk (rhabdomyolysis) has been identified in postmarketing reports with use of ledipasvir/sofosbuvir and atorvastatin. Based on the evidence from *in vitro* studies, ledipasvir and velpatasvir may have similar drug interaction potential for inhibition of OATP1B and BCRP transport, so the potential exists for sofosbuvir/velpatasvir to increase atorvastatin exposures, leading to serious adverse events. Thus, a PMR is needed to study the interaction between sofosbuvir/velpatasvir and atorvastatin in order to derive appropriate dosing recommendations for concomitant use.

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."

Reference ID: 3951086

As described in Section 1, coadministration of sofosbuvir/velpatasvir with atorvastatin is expected to increase the concentrations of atorvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. During the sofosbuvir/velpatasvir NDA review, we became aware of postmarketing reports for ledipasvir/sofosbuvir, which identified a serious safety risk (rhabdomyolysis) associated with use of ledipasvir/sofosbuvir and atorvastatin. Based on the in vitro drug interaction potential results, rosuvastatin-velpatasvir drug-drug interaction results, as well as the postmarketing reports for ledipasvir/sofosbuvir, we believe it is necessary to further investigate the potential for a drug-drug interaction between sofosbuvir/velpatasvir and atorvastatin. The objective for this PMR study is to evaluate the pharmacokinetic based drug interaction potential. The results from this study will help determine a clinical management plan, if warranted.

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.

The study is a pharmacokinetic drug interaction study. The study will be conducted in healthy volunteers.

Reference ID: 3951086

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

Reference ID: 3951086

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)

Reference ID: 3951086

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 208341

Product Name: EPCLUSA; sofosbuvir and velpatasvir fixed dose combination tablet

PMR/PMC Description: Submit the final clinical report and datasets for the ongoing trial GS-US-342-1202 (ASTRAL-5), titled "A Phase 3, Open-label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5816 Fixed Dose Combination for 12 weeks in Subjects with Chronic Hepatitis C Virus (HCV) and Human immunodeficiency Virus (HIV)-1 Coinfection," to provide safety data in HIV-1/HCV co-infected subjects receiving sofosbuvir and velpatasvir concurrently with HIV antiretroviral therapy.

PMR/PMC Schedule Milestones:

Study/Trial Completion:	8/31/2016
Final Report Submission:	12/31/2016
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-342-1202 (ASTRAL-5) is a Phase 3, open-label trial evaluating the safety and efficacy of sofosbuvir and velpatasvir (SOF/VEL) for 12 weeks in subjects with chronic HCV infection and HIV-1 co-infection. The study is ongoing during review of the NDA.

   Data obtained from GS-US-342-1202 will provide safety data in subjects receiving SOF/VEL concurrently with HIV antiretroviral therapy

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."

Reference ID: 3951086

Obtain safety data in subjects receiving SOF/VEL concurrently with HIV antiretroviral therapy and obtain dosing recommendations for HCV/HIV-1 co-infected patients.

Several phase 1 drug-drug interaction studies were conducted to evaluate the effects of co-administration of SOF/VEL with antiretroviral agents. Notable results from these trials include:

- Significant reductions in VEL AUC when coadministered with efavirenz. Since lower VEL exposures may result in lack of efficacy, co-administration of SOF/VEL with EFV containing regimens is not recommended.
- Increases in tenofovir exposures when SOF/VEL is coadministered with a tenofovir containing regimen. This effect was most notable when the antiretroviral regimen also contained ritonavir or cobicistat. It is unclear whether the increased tenofovir exposure increases risk of tenofovir-associated toxicity, particularly renal toxicity.

Study GS-US-342-1202 (ASTRAL 5) is an ongoing trial evaluating the safety and efficacy of SOF/VEL in HCV/HIV coinfected subjects. Submission of the final clinical report and datasets are identified as a PMR in order to provide safety data in subjects receiving SOF/VEL concurrently with HIV antiretroviral therapy 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.

Reference ID: 3951086

This trial is an ongoing phase 3 trial in HCV/HIV-1 coinfected 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

Reference ID: 3951086

- ☐ 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

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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)

Reference ID: 3951086

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 # 208341

Product Name: EPCLUSA; sofosbuvir and velpatasvir fixed dose combination tablet

PMR/PMC Description: Conduct a trial in hepatitis C virus genotype 3 infected subjects with cirrhosis treated with sofosbuvir and velpatasvir to determine if the addition of ribavirin improves the efficacy (i.e., sustained virologic response rate) and reduces the rate of virologic failure.

PMR/PMC Schedule Milestones:

Study/Trial Completion:	6/30/2017
Final Report Submission:	6/30/2018
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

Reference ID: 3951086

The results of the ASTRAL-3 trial demonstrate that treatment with 12 weeks of sofosbuvir and velpatasvir (SOF/VEL) for subjects with HCV GT3 provides superior SVR12 rates than the comparator, SOF + RBV for 24 weeks: 95% versus 80%, respectively. These outcomes are among the best observed in clinical trials of GT3 patients performed thus far and support labeling of SOF/VEL for 12 weeks for the treatment of GT3 HCV infection. However, certain GT3 subgroups are more likely to achieve SVR12 than others; 98% of treatment-naïve, noncirrhotic subjects achieved SVR12, whereas 89% of treatment-experienced cirrhotic subjects achieved SVR12. Overall, 97% of non-cirrhotic subjects achieved SVR12 with 12 weeks of SOF/VEL, compared to 91% of cirrhotic subjects.

Virologic failure was associated with the emergence of VEL-resistant HCV populations, which may also be cross-resistant to other drugs in the same class (NS5A inhibitors) and limit re-treatment options. Therefore, it is important that treatment with SOF/VEL is optimized to limit the rate of virologic failure and treatment-emergent drug resistance, particularly for patients with cirrhosis who may experience further deterioration of liver function if treatment is unsuccessful.

The addition of ribavirin to SOF/VEL may improve the likelihood of achieving SVR12 among cirrhotic subjects; however, treatment with SOF/VEL + ribavirin was not evaluated in ASTRAL-3. Data from a clinical trial evaluating the SOF/VEL versus SOF/VEL + ribavirin will help inform whether the addition of ribavirin can mitigate the risk of treatment failure and the development of resistance-associated polymorphisms that limit future treatment options.

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."

As noted above, approximately 9% of cirrhotic subjects in the ASTRAL-3 trial experienced virologic failure, compared to 3% of subjects without cirrhosis, following 12 weeks of treatment with SOF/VEL. Virologic failure was associated with the emergence of HCV populations carrying an NS5A Y93H coding substitution (as well as other resistance-associated substitutions) that confers viral resistance to VEL and may also confer cross-resistance to other NS5A inhibitors, limiting potential re-treatment options. Therefore, it is important that treatment with SOF/VEL is optimized in the cirrhotic population to reduce the rate of virologic failure and treatment-emergent drug resistance.

It has been shown with other HCV combination antiviral therapies and patient populations that the addition ribavirin can improve efficacy and reduce the rate of virologic failure, which in turn reduces the rate of drug resistance emergence in the treated population. Data from a clinical trial evaluating the SOF/VEL versus SOF/VEL + ribavirin will help inform whether the addition of ribavirin can mitigate the risk of treatment failure and the development of resistance-associated polymorphisms that limit future treatment options.

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

Reference ID: 3951086

- **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.

We recommend the sponsor conducts a comparative trial of SOF/VEL versus SOF/VEL + ribavirin to determine if the addition of ribavirin reduces the probability of virologic failure and the subsequent development of drug resistance in HCV genotype 3 infected patients with cirrhosis.

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)

  _____

Reference ID: 3951086

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

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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)

Reference ID: 3951086

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 # 208341

Product Name: EPCLUSA; sofosbuvir (SOF) and velpatasvir (VEL) fixed dose combination tablet

PMR/PMC Description: Collect, analyze, and submit data from the HCV infected subjects with decompensated Child-Pugh Turcotte (CPT) C cirrhosis treated with sofosbuvir/velpatasvir regimen to obtain safety data in a broader decompensated cirrhosis population (genotype 1-6 HCV infection).

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	08/31/2016
	Study/Trial Completion:	05/31/2018
	Final Report Submission:	05/31/2019
	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

Reference ID: 3951086

At present, there are limited available treatment options for chronic hepatitis C (CHC) patients with decompensated cirrhosis, particularly for patients with CHC non-genotype (GT) 1 infection. This SOF/VEL NDA submission includes a trial conducted in subjects with decompensated cirrhosis (ASTRAL-4). In ASTRAL-4 eligible subjects with CHC GT 1, 2, 3, 4, 5 or 6 infection and Child-Pugh Turcotte (CPT) B cirrhosis at screening who had not had a liver transplant were randomized to one of three SOF/VEL-containing regimens. Approximately 10% ASTRAL-4 subjects who were CPT B at screening were subsequently CPT A or C at baseline, reflecting the dynamic changes in CPT parameters over time. The CPT score is a composite score based on laboratory parameters (total bilirubin, albumin, INR) and physical examination findings (presence or absence of encephalopathy and ascites) and is used worldwide to stage the clinical severity of a patient with cirrhosis. Higher CPT scores correlate with increased mortality. The use of CPT score has limitations due to inclusion of the subjective variables ascites and encephalopathy, which are influenced by medical therapy.

A SOF/VEL plus ribavirin (RBV) 12 week regimen is recommended for CHC treatment in patients with decompensated cirrhosis based upon ASTRAL-4 data. Despite limited number of subjects with baseline CPT C cirrhosis enrolled in the trial, the review team supports extending the SOF/VEL+RBV 12 Week dosing recommendation to both the CPT B and C populations, populations in need of additional CHC treatment options. This recommendation is based upon consideration of decompensated cirrhosis as a spectrum of disease progression rather than two discreet sub-populations of CPT B and CPT C. Furthermore, no dose-exposure or unique safety issues were identified based on these limited data in ASTRAL-4 precluding SOF/VEL+RBV use in the CPT C population. We are requiring data submission postapproval evaluating the safety of SOF/VEL-containing regimen in the population with decompensated CPT C cirrhosis because of the small overall number of subjects with baseline CPT C cirrhosis in ASTRAL-4. The Applicant plans to conduc (b) (4) trial to evaluate the safety of SOF/VEL+RBV 12 week regimen in approximately (b) (4) subjects with CHC infection and decompensated CPT C cirrhosis. These data will provide in mation about the safety of SOF-VEL-containing treatment in a broader decompensated cirrhosis population (genotype 1-6 HCV infection).

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

The pertinent clinical issues are described in the response to #1. The goal of the trial will be to evaluate safety of SOF/VEL+RBV 12 week regimen in subjects with CHC infection and decompensated CPT C cirrhosis, including identification of serious adverse events regarding progression of liver disease, liver-related mortality or liver failure requiring transplantation.

Reference ID: 3951086

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.

   The Applicant plans to conduct a [redacted] (b) (4) study to evaluate the safety of SOF/VEL+RBV for 12 weeks in HCV infected subjects with decompensated CPT C cirrhosis. [redacted] (b) (4)

   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

Reference ID: 3951086

☐ 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

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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)

Reference ID: 3951086

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 # 208341

Product Name: EPCLUSA; sofosbuvir (SOF) and velpatasvir (VEL) fixed dose combination tablet

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

PMR/PMC Schedule Milestones:

Final Protocol Submission:	
Study/Trial Completion:	01/31/2022
Final Report Submission:	01/31/2023
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

At present, there are limited available treatment options for chronic hepatitis C (CHC) patients with decompensated cirrhosis, particularly for patients with CHC non-genotype 1 infection. This SOF/VEL NDA submission includes a trial conducted in subjects with decompensated cirrhosis, ASTRAL-4, and these data support a recommendation for a SOF/VEL-containing regimen in patients with CHC genotype 1, 2, 3, 4, 5 or 6 infection with decompensated cirrhosis. The approval relies on efficacy measured as sustained virologic response (SVR) at 12 weeks posttreatment, SVR12 being an accepted benchmark of CHC virologic cure. We are requesting commitment to submit in the postmarketing period data evaluating the durability of virologic response in the population with cirrhosis, including decompensated cirrhosis. Additionally, we are requesting commitment to submit in the postmarketing period data evaluating the longer term impact of SVR on important clinical outcomes including progression or regression of liver disease, liver-related mortality, occurrence of hepatocellular carcinoma, or liver failure requiring liver transplantation. These data will provide information about the impact of CHC treatment on clinical endpoints in patients with cirrhosis, including decompensated cirrhosis.

Reference ID: 3951086

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

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

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

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

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

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

  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

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

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

Reference ID: 3951086

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

Reference ID: 3951086

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)

Reference ID: 3951086

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 # 208341
Product Name: Sofosbuvir/velpatasvir

PMR/PMC Description: Please conduct site-directed mutant phenotypic analyses of sofosbuvir against an HCV genotype 3 replicon with the following substitutions: NS5B_L314F, NS5B_L314I, and NS5B_L314P.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	N/A
	Study/Trial Completion:	N/A
	Final Report Submission:	02/28/2017
	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

   Additional treatment-emergent substitutions were identified from virologic failures in the sponsor's clinical studies. The sponsor will need to phenotypically characterize these.

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."

Reference ID: 3951086

The impact of these substitutions on the antiviral activity of sofosbuvir needs to be evaluated to understand the possible impact on efficacy.

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 site-directed mutant phenotypic analyses of sofosbuvir against an HCV genotype 3 replicon with the following substitutions: NS5B_L314F, NS5B_L314I, and NS5B_L314P.

Reference ID: 3951086

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)
The impact of these substitutions on the antiviral activity of sofosbuvir needs to be evaluated to understand the possible impact on efficacy.

☐ 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

Reference ID: 3951086

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.*

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(signature line for BLAs)

Reference ID: 3951086

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
06/24/2016

POONAM MISHRA
06/24/2016

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:	June 7, 2016
Requesting Office or Division:	Division of Antiviral Products (DAVP)
Application Type and Number:	NDA 208341
Product Name and Strength:	Epclusa (sofosbuvir and velpatasvir) Tablets 400 mg/100 mg
Submission Date:	May 18, 2016
Applicant/Sponsor Name:	Gilead Sciences, Inc.
OSE RCM #:	2015-2433-1
DMEPA Primary Reviewer:	Mónica Calderón, PharmD, BCPS
DMEPA Team Leader:	Vicky Border-Hemphill, PharmD

1 PURPOSE OF MEMO

Gilead Sciences, Inc has submitted the revised container labels (Appendix A) for Epclusa in response to recommendations we made during a previous label and labeling review. [1] Thus, the Division of Antiviral Products (DAVP) requested that we review the revised label and labeling to determine if it is acceptable from a medication error perspective.

2 CONCLUSIONS

The Sponsor revised the container label as well as the Gilead Access Program container label and carton labeling according to all of DMEPA's recommendations. They are acceptable and we have no further recommendations at this time.

~~APPENDIX A. LABEL AND LAB~~ELING SUBMITTED ON MARCH 2, 2016

[1] Calderon M. Label and Labeling Review for Epclusa (NDA 208341). 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); 2016 Mar 02. 32 p. OSE RCM No.: 2015-2433.

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/s/

MONICA M CALDERON
06/07/2016

BRENDA V BORDERS-HEMPHILL
06/08/2016

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

PATIENT LABELING REVIEW

Date:	May 20, 2016
To:	Debra Birnkrant, MD Director **Division of Antiviral Products (DAVP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA, CPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Sam Skariah, PharmD, RAC Team Leader, Division 1 **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	EPCLUSA (sofosbuvir and velpatasvir)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 208341
Applicant:	Gilead Sciences, Inc.

1 INTRODUCTION

On October 28, 2015, Gilead Sciences, Inc. submitted for the Agency's review a New Drug Application (NDA) 208341 for EPCLUSA (sofosbuvir and velpatasvir) tablets. The proposed indication for EPCLUSA (sofosbuvir and velpatasvir) is for the treatment of adult patients with chronic hepatitis C virus (HCV) infection:

- without cirrhosis or with compensated cirrhosis
- with decompensated cirrhosis for use in combination with ribavirin.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antiviral Products (DAVP) on December 10, 2015, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for EPCLUSA (sofosbuvir and velpatasvir) tablets.

2 MATERIAL REVIEWED

- Draft EPCLUSA (sofosbuvir and velpatasvir) tablets PPI received on October 28, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 6, 2016.
- Draft EPCLUSA (sofosbuvir and velpatasvir) tablets Prescribing Information (PI) received on October 28, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 6, 2016.
- Approved Harvoni (sofosbuvir and ledipasvir) comparator labeling dated February 12, 2016.

3 REVIEW METHODS

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

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

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

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

MORGAN A WALKER
05/20/2016

SAMUEL M SKARIAH
05/20/2016

BARBARA A FULLER
05/20/2016

Clinical Inspection Summary

Date	May 12, 2016
From	Antoine El Hage
To	Linda Onaga, Regulatory Project Manager Prabha Viswanathan, Medical Reviewer Kim Struble, PharmD, CTDL Division of Antiviral Products
NDA/BLA #	NDA 208341/ SDN 000 and 001
Applicant	Gilead Sciences, Inc.
Drug	Sofosbuvir/Velpatasvir
NME (Yes/No)	Yes
Therapeutic Classification	Priority
Proposed Indication(s)	Treatment of chronic hepatitis C infection (CHC)
Consultation Request Date	12/16/2015
Summary Goal Date	May 15, 2016
Action Goal Date	June 28, 2016
PDUFA Date	June 28, 2016

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection of this NDA consisted of two foreign clinical sites and six domestic sites as well as the sponsor. In general, based on the inspections of the eight clinical sites and the sponsor, the inspectional findings support reliability or validity of data as reported by the sponsor under this NDA.

The inspection of three clinical investigators (Drs. Younes, Nguyen, and Dore) revealed regulatory violations. Although regulatory violations were noted, they are unlikely to significantly impact primary safety and efficacy analyses.

The preliminary classification for Drs. Tran, Morgan, Luetkemeyer, and Vargas is No Action Indicated (NAI). The final classification for Dr. Roberts is No Action Indicated (NAI).

No regulatory violations were noted during the sponsor inspection of the four sites listed and covered during the inspection. The preliminary classification for the sponsor is No Action Indicated (NAI .

All pending classifications are considered preliminary until the final communication letter is sent to the inspected party.

II. BACKGROUND

Velpatasvir (VEL-GS-5816) is a novel HCV NS5A inhibitor that has demonstrated a potent anti-HCV activity against all genotypes. More than 1000 HCV infected subjects have been dosed with GS-5816 in ongoing Phase 2 clinical studies; the sponsor states that these studies demonstrated that co-administration of Sofosbuvir (SOF) 400 mg with GS-5816 100 mg for 12 weeks is well tolerated and results in high SVR across a broad range of HCV genotypes. The applicant has co-formulated SOF 400 and GS5816 100 mg into a single agent administered together as an oral tablet. The claim of a fixed –dose combination may have a major impact on the global prevalence and burden of HCV as it may represent a simple, well-tolerated, highly efficacious pan-genotype treatment for ALL HCV infected subjects. The Applicant is seeking treatment of adults with chronic genotype 1, 2, 4, 5, or 6 hepatitis C virus HCV infection.

GS-5816 is an oral formulation fixed combination, available in these studies as a 100 mg tablet.

The Applicant-sponsored four studies: Study Protocols GS-US-342-1138 for treatment of all genotypes, GS-US-342-1139 for treatment of genotype 2 HCV-infected subjects, GS-US-342-1140 for treatment of genotype 3 HCV subjects , and GS-US-342-1137 for the treatment of subjects with HCV infection of all genotypes and with Child-Pugh Class B cirrhosis were submitted in support of the application.

Inspections were requested for the following clinical studies:

Protocol GS-US-342-1138

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Safety and Efficacy of Sofosbuvir/ GS-5816 Fixed-Dose Combination for 12 Weeks in Subjects With Chronic Hepatitis C (HCV)" (ASTRAL-1).

The primary objectives of this study were: 1) to evaluate the efficacy of treatment with SOF/GS-5816 for 12 weeks in subjects with chronic HCV infection as measured by the proportion of subjects with SVR 12, and 2) to evaluate the safety and tolerability of treatment with SOF/GS-5816 for 12 weeks.

This protocol was an international, randomized, multicenter, double-blind, placebo-controlled study to evaluate the safety, tolerability, and antiviral efficacy of sofosbuvir/GS-5816 FDC with SOF/GS-5816 placebo administered for 12 weeks in subjects with chronic genotype 1, 2, 4, 5 or 6 HCV infection. A target of 600 subjects with documented chronic genotype 1, 2, 4, 5, or 6 HCV infections were randomized. Approximately 20 % of the subjects were treatment experienced and 20% of subjects had cirrhosis. Subjects with genotype 1, 2, 4, and 6 HCV infection (and subjects with HCV genotype indeterminate) were randomized in a 5:1 in a double-blind manner to either treatment groups:

- Group 1: FDC tablet (SOF 400 mg/GS-5816 100 mg) once daily for 12 weeks
- Group 2: FDC tablet (SOF mg/GS-5816 mg) placebo once daily for 12 weeks

Subjects were randomized by genotypes and the presence or absence of cirrhosis at screening. Subjects with any liver disease of non-HCV etiology or with human immunodeficiency virus (HIV) or hepatitis B co-infection or malignancy or transplantation were excluded.

Number of subjects: 741 randomized
Number of sites: 81
Participant countries: Both US, Canada, Europe, and Asia
First subject screened: July 18, 2014
Last subject observation for efficacy endpoint: June 26, 2015

Protocol GS-US-342-1139

A Phase 3, Multicenter, Randomized, Open-Label Study to Compare the Safety and Efficacy of Sofosbuvir/GS-5816 Fixed-Dose Combination for 12 Weeks With Sofosbuvir/and Ribavirin for 12 Weeks in Subjects With Chronic Genotype 2 HCV Infection" (ASTRAL-2).

The primary objectives of this study were: 1) to compare the efficacy of treatment with sofosbuvir (SOF)/velpatasvir (VEL, GS-5816) for 12 weeks with that of SOF+ ribavirin (RBV) for 12 weeks as measured by the proportion of subjects with sustained virologic response (SVR) 12 weeks after cessation of treatment (SVR12), and 2) to evaluate the safety and tolerability of each treatment regimen.

This study was an ongoing phase 3, randomized, open-label, multicenter study assessed the antiviral efficacy, safety, and tolerability of 12 weeks of SOF/VEL treatment compared with 12 weeks of SOF+RBV treatment in subjects with chronic genotype 2HCV infection. Approximately 240 subjects were randomized (1:1) to one of the following 2 treatment groups:

- Group 1 SOF/VEL 12 weeks FDC tablet (SOF 400 mg/VEL 100mg) once daily for 12 weeks
- Group 2 SOF+RBV 12 weeks FDC tablet (SOF 400 mg once daily+ RBV (1000- 1200 mg/day divided twice daily) tablets for 12 weeks

Randomization was stratified by the presence or absence of cirrhosis at screening and prior treatment experience (treatment naïve [vs] treatment experienced). Approximately 20% of the subjects were treatment experienced and approximately 20% of subjects had cirrhosis. Subjects were stratified as genotype 2. Post treatment HCV RNA results were blinded to the investigator.

Subjects with any liver disease of non-HCV etiology or with human immunodeficiency virus (HIV) or hepatitis B co-infection were excluded.

Number of subjects: 269 randomized

Number of sites: 51
Participant countries: Only U.S.
First subject screened: September 22, 2014
Last subject observation for the report: June 9, 2015

Protocol GS-US-342-1140

A Phase 3, Multicenter, Randomized, Open-Label Study to Compare the Safety and Efficacy of Sofosbuvir/GS-5816 Fixed-Dose Combination for 12 Weeks With Sofosbuvir/and Ribavirin and 24 Weeks in Subjects With Chronic Genotype 3 HCV Infection" (ASTRAl-3).

The primary objectives of this study were 1) to compare the efficacy of treatment with sofosbuvir (SOF)/velpatasvir (VEL, GS-5816) for 12 weeks with that of SOF+ ribavirin (RBV) for 12 weeks as measured by the proportion of subjects with sustained virologic response (SVR) 24 weeks as measured by the proportion of subjects with sustained virologic response (SVR) 12 weeks after cessation of treatment (SVR12), and 2) to evaluate the safety and tolerability of each treatment regimen.

This study was an ongoing phase 3, randomized, open-label, multicenter study which assessed the antiviral efficacy, safety, and tolerability of 12 weeks of SOF/VEL treatment compared with 24 weeks of SOF+RBV treatment in subjects with chronic genotype 3 HCV infection. Approximately 558 subjects were randomized (1:1) to one of the following 2 treatment groups:

- Group 1 SOF/VEL 12 weeks FDC tablet (SOF 400 mg/VEL 100mg) once daily for 12 weeks
- Group 2 SOF+RBV 12 weeks FDC tablet (SOF 400 mg once daily+ RBV (1000- 1200 mg/day divided twice daily) tablets for 24 weeks

Randomization was stratified by the presence or absence of cirrhosis at screening and prior treatment experience (treatment naïve [vs] treatment experienced). Approximately 20% of the subjects were treatment experienced and approximately 20% of subjects had cirrhosis. Subjects were stratified as genotype 3. Post treatment HCV RNA results were blinded to the investigator.

Subjects with any liver disease of non-HCV etiology or with human immunodeficiency virus (HIV) or hepatitis B co-infection were excluded.

Number of subjects: 558 randomized
Number of sites: 76
Participant countries: Both U.S. and worldwide
First subject screened: 7/14/2014
Last observation report: 9/8/2015
Last subject observation for the efficacy endpoint: 9/1/2015

Protocol GS-US-342-1137

A Phase 3, Multicenter, Open-Label Study to investigate the Efficacy and Safety of Sofosbuvir/GS-5816 Fixed –Dose Combination in Subjects With Chronic HCV Infection and Child-Pugh Class B Cirrhosis" (ASTRAL-4).

The primary objectives of this study were: 1) to evaluate the efficacy of treatment with SOF/GS-5816 FDC with and without RBV for 12 weeks and SOF/GS-5816 for 24 weeks in subjects with chronic HCV infection and CPT class-B cirrhosis as measured by the proportion of subjects with sustained viral response 12 weeks after cessation of treatment (SVR12), and 2) to evaluate the safety and tolerability of each treatment regimen.

This study was a multicenter, randomized, open –label study that evaluated the safety, tolerability and antiviral efficacy of SOF/GS-5816 FDC with and without RBV for 12 weeks and SOF/GS-5816 FDC for 24 weeks in subjects with chronic genotypes 1-6 HCV infection with CPT class B (score 7-9) cirrhosis. Eligible subjects were randomized (1:1:1) to:

1. Group 1 (n=50): SOF/GS-5816 for 12 weeks or
2. Group 2 (n=50): SOF/GS-5816 + RBV for 12 weeks or
3. Group 3 (n=50): SOF/GS-5816 for 24 week

Number of subjects: 267
Number of sites: 47
Participant countries: Only U.S.
First subject screened: 7/31/2014
Last observation for this report: 9/8/2015
Last subject observation for the primary efficacy endpoint: 8/25/2015

All four trials were conducted in subjects with CHC and all utilized the same primary endpoint. Trial design was similar across studies but differed by HCV genotype (GT) and cirrhosis status: ASTRAL-1 evaluated subjects with GT 1, 2,,4,5, or 6 HCV infection who were non-cirrhotic or had compensated cirrhosis; ASTRAL-2 evaluated subjects with GT2 HCV infection who were non-cirrhotic or had compensated cirrhosis: ASTRAL-3 evaluated subjects with GT3 HCV infection who were non-cirrhotic or had compensated cirrhosis; and ASTRAL-4 evaluated subjects with GT-6 HCV infection and decompensated cirrhosis. According to the sponsor, the proportion of subjects treated with SOF/VEL, who met the primary endpoint was high across all four trials, with 99% of subjects achieving SVR12 in ASTRAL-1 and 2, 95% in ASTRAL-3, and 86-94% in ASTRAL-4.
The CDER review division team with input from statistics was involved in the selection process. The sites were chosen principally due to high patient accrual across multiple protocols.

III. RESULTS (by site):

Name of CI, Site #, Address, Country if non-U.S. or City, State if U.S.	Protocol # and # of Subjects	Inspection Date	Classification
Tram Tran, M. D 89000 Beverly Blvd. Suite 250 Los Angeles, CA 90048 Site #1589	Astral-1 GS-US-342-1138 Subjects enrolled: 18	2/23-25/2016	NAI
Mindie Nguyen, M.D 750 Welch Rd., Suite 210 Palo Alto, CA 94304 Site #4078	Astral-1 GS-US-342-1138 Subjects enrolled: 8	3/7-10/2016	VAI
Anne Luetkemeyer, M.D. University Of California SF San Francisco, CA 94110 Site #3317	Astral-2 GS-US-342-1139 Subjects enrolled: 6	5/9-12/2016	Interim Classification NAI
Timothy Morgan, M.D. VA Long Beach Healthcare 5901 East Seventh St Long Beach, CA 90822 Site #5667	Astral-2 GS-US-342-1139 Subjects enrolled: 8	1/21-27/2016	Interim classification NAI
Stuart Roberts, M.D. The Alfred Hospital 99 Commercial Rd. Melborne, VIC 3004 Australia Site #1126	Astral-3 GS-US-342-1140 Subjects enrolled: 14	3/7-11/2016	NAI
Greg Dore, M.D. St. Vincent's Hospital Sydney 390 Victoria St. Darlinghurst, NSW 2010 Australia Site #1815	Astral-3 GS-US-342-1140 Subjects enrolled: 10	3/14-17/2016	VAI
Ziad Younes, M.D. Gastro One 1310 Wolf Park drive Germantown, TN 38138 Site #3060	Astral-4 GS-US-342-1137 Subjects enrolled: 5	1/12-15/2015	VAI
Hugo E. Vargas, M.D. Mayo Clinic Arizona Hospital 5777 East Mayo Blvd. Phoenix, AZ 85054 Site #3055	Astral-4 GS-US-342-1137 Subjects enrolled: 5	2/28-3/1/2016	Interim classification NAI
Gileads Sciences, Inc 333 Lakeside Drive Foster city, CA 94404 Sites #4078,5667, 1815,3055	Protocols 1138,,1139, 1140 &1137 Total subjects: 48	4/7-14/2016	Interim classification NAI

Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

NOTE: Site inspections focused on review of informed consent documents, IRB and ethics committee correspondence, financial disclosures, training records, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, vital signs, subject source documents, including medical history records, drug accountability, and the use of concomitant medications. Source documents were compared to data listing for primary efficacy endpoints and adverse events reporting.

1. **Tram Tran, M.D. (Site #1589)**

   Records were organized and legible. Medical records/source documents were compared to case report forms and data listing for primary efficacy endpoints and adverse events reporting. No deficiencies were found.

   There were 22 subjects screened, four subjects were reported as screen failures, and 18 subjects were enrolled in the study. All 18 subjects completed the study. The medical records for all subjects were reviewed. The audit revealed adequate adherence to the regulations and investigational plan. There were no objectionable conditions noted and no Form FDA 483 was issued. The IRB ([redacted] (b) (4)) directed Dr. Tran not to personally consent or screen the subjects and she complied.

   The data generated by this site appear acceptable. The inspection did not indicate serious deviations/findings that would impact the acceptability of the data submitted in support of the application

2. **Mindie Nguyen, M.D./Site #4078**

   Record*s* were organized and legible. Medical records/source documents were compared to data listing for primary efficacy endpoint and adverse events reporting. The HCV/RNA IU/mL results were not available at the site for subsequent visits (as per protocol requirements).

   There were 10 subjects screened, two subjects were reported as screen failures, and the reasons were documented. Eight subjects enrolled in the study and all eight completed the study. The ORA investigator compared the laboratory results/values on the data listing with the central laboratory results on files, and was able to verify the data for the screening, baseline, Weeks 1, 6, and 12 results for all the eight subjects reviewed. No discrepancies were found.

Not all concomitant medications were reported in the case report forms and subsequently to the sponsor. In addition, there was no documentation to show the use of concomitant medication by certain subjects was discontinued during the study. For example, Subject #63264 received omeprazole, a disallowed medication, and it was reported as being discontinued on 10/12/2014. However, subsequent progress notes for certain visits on 11/3/2014, 11/13/2014, 12/2/2014, and 12/15/2014 all listed omeprazole as a current outpatient prescription. There was no documentation to show the drug was discontinued for Subject 63264. The record was annotated to indicate the patient "states she was mistaken". The clinical investigator stated that the record is correct and the patient was not taking omeprazole. Similar concomitant medication use was noted for Subject 63236.

The clinical investigator stated the source documents were incorrect, but there was no documentation that the medications were discontinued. The clinical investigator promised to remedy the situation in future studies.

The ORA investigator noted that Subject 63694 was ineligible for enrollment because the Subject's partner was 4 months pregnant at the time of screening. The protocol exclusion #5 states/reads "Pregnant or nursing females or male with pregnant female partner" should be excluded. Although the pregnancy was known at the time of screening, the subject was enrolled in the study. The clinical investigator stated that she informed the IRB and the sponsor .The medical monitor "signed a form regarding the protocol deviation indicating the subject was to be counseled but not discontinued". Technically, this is a protocol deviation.

Inadequate record keeping practices was discussed with the clinical investigator specifically the missing respiratory values for certain subjects. Vital signs were required by the protocol and were performed by medical assistants at the clinic who entered the results into the electronic medical record system. The study coordinator was asked how the respiration is measured when the medical assistant did not measure respiration rate. The study coordinator stated he watches the patient's respiration for 20 seconds and multiplied by 3 to get the rate. The ORA investigator informed the clinical investigator that she counted less than 10 times the respiration rate was documented in the electronic progress notes. The value ranged from 12-20. The ORA investigator found more than eighty progress notes that included vital signs, but the respiratory rate was missing. The ORA investigator suggested that the clinical investigator review the process of obtaining the respiration rate to ensure the results are accurate. It is not clear from the available source documents the individual(s) who performed and recorded the vital signs. Dr. Nguyen was reminded that the data need to be attributable to the person performing the work or collecting the data. The clinical investigator added she will work to improve documentation in the electronic records.

Although deviations were found at the site, it is unlikely that the findings significantly impacted the outcome of the study. Overall, the data generated at Dr. Nguyen's in support of clinical efficacy and safety is considered acceptable and may be used in support of the pending application.

3. **Anne Luetkemeyer, M.D./Site #3317**

Records were organized and legible. Medical records/source documents were compared to case report forms and data listings for the primary efficacy endpoints and adverse events reporting. Minor deviations were noted regarding Subjects 65127 and 65124 who were on protocol-restricted concomitant medications to treat depression at the time of enrollment, and therefore met exclusion criteria. This was properly reported to the IRB and the sponsor. The clinical investigator discussed the use of the medications with the sponsor who agreed to allow the subjects to continue on the study to maintain steady state. The clinical investigator stated that there were no concerns from a drug-drug interaction standpoint. Her response appears acceptable.

There were nine subjects screened, three subjects were reported as screen failures, and six subjects were enrolled. Five subjects reached post-treatment phase, and one subject withdrew prior to receiving any treatment with study drug. All five subjects completed the study. The medical records for all subjects were reviewed. The inspection revealed adequate adherence to the regulations and investigational plan. There were no objectionable conditions noted and no Form FDA 483, Inspectional Observations was issued to Dr. Luetkemeyer. The ORA investigator discussed with the clinical investigator that study medications stored in a cabinet that non-study personnel had access to as they share space with the clinic should be avoided. This observation/finding had no significant impact on the study results.

With the exception of the deviations noted above, the data generated by this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

4. **Timothy Morgan, M.D./Site #5667**

Records were organized and legible. Medical records/source documents were compared to case report forms and data listings for primary efficacy endpoint and adverse events reporting. No deficiencies were noted.

There were eight subjects screened and all eight subjects were enrolled. There were no withdrawals/discontinuation or early termination. All eight subjects completed the study. The medical records for all subjects were reviewed. The inspection revealed adequate adherence to the regulation and investigational plan. There were no objectionable conditions noted and no Form FDA 483, Inspectional Observations, was issued.

The data generated by this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

5. **Stuart Roberts/Site #1126**

Records were organized and legible. Medical records/source documents were compared to case report forms and data listings for primary efficacy endpoints and adverse events reporting. No deficiencies were noted.

There were 14 subjects screened and all 14 subjects were enrolled. There were two subjects who did not appear for Week 24 follow-up, and one subject did not achieve SVR 12. Eleven subjects completed the study. The medical records for all subjects were reviewed. The inspection revealed adequate adherence to the regulation and investigational plan. There were no objectionable conditions noted and no Form FDA 483, Inspectional Observations, issued. The ORA investigator noted instances of write overs, one missed laboratory result (HCV viral load at baseline visit), and no documentation of follow-up on two missed ECGs.

Although minor discussion points were noted at the site, it is unlikely that these findings significantly impacted the outcome of the study. Overall, the data generated at Dr. Robert's site in support of the clinical efficacy and safety is considered acceptable and may be used in support of the application.

6. **Greg Dore, M.D./Site #1815**

Records in general were not organized, but were made available upon request. The data provided was legible and verifiable. Medical records/source documents were compared to case report forms and data listings for primary efficacy endpoints and adverse events reporting. Minor protocol deviations were noted.

At this site, a total of 13 subjects were screened, three subjects were reported as screen failures, 10 subjects were enrolled, and four subjects were discontinued after enrollment. One subject discontinued due to an adverse event, one subject did not return after Week 16, and two subjects did not achieve SVR 12. Six subjects completed the study.

The medical records for all subjects were reviewed. At the conclusion of the inspection, no FDA 483 was issued to Dr. Dore. However, the ORA investigator noted and discussed with the clinical investigator the following deviations:

Subjects 62181 and 62172 did not meet inclusion criterion # 8. "Liver imaging within 6 months of Baseline/Day1 is required in patients with cirrhosis to exclude hepatocellular carcinoma". There was no documentation available to show that imaging was performed. In addition, Subject 62170 had Fibro Test score >0.75 and APRI >2 at screening which is an indication of cirrhotic based on Fibroscan results. The clinical investigator made the determination that the subject was non-cirrhotic based on screening Fibroscan result of 12.0 kpa. The clinical investigator agreed with the finding that imaging was not performed within the required 6 months window and he believes that the safety of the subjects was not compromised. In addition, the clinical investigator stated that the record keeping was not ideal and he will work on better record keeping practices in the future. His verbal response

was determined to be acceptable.

Although minor deviations were noted at the site, it is unlikely that these findings significantly impacted the outcome of the study. Overall, the data generated at Dr. Dore's site in support of the clinical efficacy and safety is considered acceptable and may be used in support of the application.

7. **Zaid Younes, M.D. Site #3060**

There were 5 subjects screened at this site. Five subjects were randomized into the study, one subject was lost to follow-up, and two subjects completed the study and achieved SVR 12. All subject records were reviewed. There were two deaths reported at this site.

At the conclusion of the inspection, a one-item Form FDA 483 was issued to Dr. Younes. The ORA investigator noted failure to adhere to the investigational plan. The violation included the following:

Protocol Section 4.2, reads "Subjects must meet all the following inclusion criteria to be eligible for participation in this study". For example:

Subject #64200 did not meet inclusion criterion #4 which states that subjects must have chronic HCV infection greater or equal to 6 months as documented by either prior medical history or liver biopsy for enrollment. The Screening Visit Worksheet dated 10/31/2014 indicated that Hepatitis C was first documented in the medical records for this subject on 9/22/2014.

This subject was allowed to enroll in the study contrary to inclusion criterion #4. In addition, the same subject had a documented history which showed that the subject drank a six pack of beer daily for the past two years.

The Social History sections states "that the subject drinks 5 to15 drinks per week". Furthermore, the Central Laboratory used for this study documented the use of oxycodone via urinalysis result was flagged to exclude the subject for illegal drug use. The clinical investigator stated that the prescribed drug was for pain. However, there was no documentation available to indicate when and how long the subject was taking this medication.

With the exceptions noted above, the medical records reviewed were found to be in order, organized and the data verifiable. The clinical investigator acknowledged the deviation and stated that even though the subject did not have a documented diagnosis of Chronic HCV infection for greater than or equal to six months by either medical history or liver biopsy, Dr. Younes stated that in his medical judgment, the scarring of the liver and diagnosis of cirrhosis are the factors that allowed him to enroll the subject in the study. Dr. Younes added that whether the subject had a clinically relevant history of alcohol or drug abuse within 12 months of screening was likely due to an error in transcription of the subjects'

medical records by the referring physician.

Although minor deviations were noted at the above site, it is unlikely that this finding significantly impacted the outcome of the study. Overall, the data generated at Dr. Youne's site in support of the clinical efficacy and safety is considered acceptable and may be used in support of the application.

8. **Hugo Vargas, M.D./Site# 3055**

Records were well organized and the data verifiable. The medical records/source documents were compared to case report forms and data listings for efficacy endpoints and adverse events reporting. There were five subjects screened. Two subjects were reported as screen failures, three subjects enrolled into the study, and two subjects completed the study. There was no under-reporting of serious adverse events. However, Subject 64020 experienced shortness of breath and chest pain which were reported in the e-CRF, but not included in the data listings. This appears tobe an isolated event

The primary efficacy endpoints were verifiable. At the conclusion of the inspection no Form FDA 483, Inspectional Observations, was issued to Dr. Vargas.

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

9. **Gilead Sciences, Inc./Sites #4078, 5667,1815, and 3055**

Gilead is a U.S. corporation located in Foster City, CA. The inspection audited the four protocols and focused on the clinical investigators listed above during the course of the sponsor-monitor inspection. The inspection reviewed the following; company history, organizational structure and staff responsibilities, transfer of obligation, communications with contractors, financial disclosures, data management, protocol adherence , adverse events reporting, drug accountability, monitoring, SOPs, training program, and all site documents pertaining to the four sites inspected.

At the conclusion of the inspection, no form FDA 483 was issued to the firm. The inspection found that the sponsor adhered to their SOPs regarding proper monitoring of their clinical investigator. The activities included, but were not limited to, trial drug records, subject records, electronic database for entry of study data, protocol adherence, case report forms/source documents and adverse event reporting. Medical records reviewed were found adequate and the data verifiable. There were no death and no evidence of under-reporting of adverse events or significant protocol deviations.

Prior to study initiation, Gilead assessed the sites to determine if they were qualified for conducting the study. The monitoring practices were adequate.

The sponsor monitoring procedures appears to have been conducted adequately and the data submitted by the sponsor may be used in support of the respective indication.

CC:

Central Doc. Rm. NDA 208341/000 and 001
DAVP /Division Director/Debra Birnkrant
DAVP /Medical Team Leader/Kim Struble
DAVP /Project Manager/Linda Onaga
DAVP/Medical Officer/ Prabha Viswanathan
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/ Ni Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Susan Thompson
OSI/DCCE/GCPAB/ Reviewer/ Antoine El Hage
OSI/ GCPAB/ Program Analysts/ Yolanda Patague/ Joseph Peacock
OSI/Database PM/Dana Walters

{See appended electronic signature page}

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

CONCURRENCE:

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Susan Thompson, M.D.
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CONCURRENCE: *{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Enforcement
Office of Scientific Investigations

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/s/

ANTOINE N EL HAGE
05/13/2016

SUSAN D THOMPSON
05/13/2016

KASSA AYALEW
05/13/2016

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

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

Memorandum

Date: May 13, 2016

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

From: Kemi Asante, PharmD, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 208341
EPCLUSA™ (sofosbuvir and velpatasvir) tablets, for oral use

In response to DAVP's December 10, 2015 consult request, OPDP has reviewed the proposed package insert (PI) for EPCLUSA (sofosbuvir and velpatasvir) tablets, for oral use.

Comments on the PI are provided below and are based on the review of the substantially complete version of the PI provided by DAVP via email on May 6, 2016.

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).

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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Reference ID: 3931286

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/s/

OLUWASEUN A ASANTE
05/13/2016

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:	March 2, 2016
Requesting Office or Division:	Division of Antiviral Products (DAVP)
Application Type and Number:	NDA 208341
Product Name and Strength:	Epclusa (sofosbuvir and velpatasvir) Tablets 400 mg/100 mg
Product Type:	Multi-ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Gilead Sciences, Inc.
Submission Date:	October 28, 2015
OSE RCM #:	2015-2433
DMEPA Primary Reviewer:	Mónica Calderón, PharmD, BCPS
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

Reference ID: 3896186

1 REASON FOR REVIEW

Gilead Sciences, Inc. submitted a new drug application (NDA 208341) for the treatment of patients with chronic hepatitis C virus (HCV) infection. Thus, the Division of Antiviral Products (DAVP) requested DMEPA evaluate the Applicant's proposed full prescribing information (FPI), patient package insert (PPI) and container label. 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
Previous DMEPA Reviews	B (N/A)
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant is proposing a multi-ingredient, single-strength tablet available as, 400 mg/100 mg. The tablets will be packaged in 28-count bottles, which are supported by the dosage and administration of this product. DMEPA performed a risk assessment of the proposed commercial container label, the FPI, and PPI.

We determined that important information is displayed clearly on the proposed commercial container label, in the Dosage and Administration section within the FPI, and the "How Should I Take [TRADENAME]" section within the PPI. 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 "Gilead Access Program"; thus, the same recommendations for the commercial packaging will apply. We recommend that all labels and labeling should be updated to reflect the conditionally acceptable proprietary name, Epclusa.

Reference ID: 3896186

Medication errors with Sovaldi (sofosbuvir)
A postmarketing review for Sovaldi was completed May 30, 2014 identifying medication errors including wrong frequency and improper dose errors. Although no root cause could be determined in all cases, it was noted that some patients may be mistaking the dosing frequency of Sovaldi to be the same as ribavirin, twice daily. Changes to the container label and PPI were implemented to provide clarification and to help mitigate future medication errors in frequency and dosing.

We considered the risk for medication errors with Epclusa given the history of medication errors with Sovaldi due to both products being indicated for the treatment of HCV, and having the same dosing and frequency of administration. We recommend a statement be added to the container label to help mitigate dosing and frequency of administration medication errors. We provide recommendations in section 4.2 below.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes Gilead's proposed PPI and FPI are acceptable. However, to minimize the potential for wrong frequency and improper dosing errors, we provide recommendations to add a statement to the container label stating the dose and frequency of administration in section 4.1. We also recommend updating the FPI and labels and labeling with the conditionally acceptable proprietary name, Epclusa, where applicable. See section 4.1 and 4.2, below, for our recommendations.

4.1 RECOMMENDATIONS FOR THE DIVISION

Full Prescribing Information

1. Replace "TRADENAME" with the conditionally acceptable proprietary name, Epclusa.

4.2 RECOMMENDATIONS FOR GILEAD SCIENCES, INC.

We recommend the following be implemented prior to approval of this NDA:

Commercial Container Label and Access Container Label and Carton Labeling

1. Revise and move the usual dosage statement to the principal display panel to read similar to, "Take 1 tablet once daily". To accommodate this change, consider placing the statement above the "Note to pharmacist". Additionally, consider bolding, changing font color, or some other means to bring prominence to this statement.
2. Replace "TRADENAME" with the conditionally acceptable proprietary name, Epclusa.
3. Revise the active ingredients to read as follows, "sofosbuvir and velpatasvir".

Reference ID: 3896186

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Epclusa that Gilead Sciences, Inc. submitted on October 28, 2015.

Table 2. Relevant Product Information for Epclusa	
Initial Approval Date	N/A
Active Ingredient	sofosbuvir and velpatasivr
Indication	Treatment of chronic hepatitis C virus (HCV) infection
Route of Administration	Oral
Dosage Form	Tablet
Strength	400 mg/100 mg
Dose and Frequency	One tablet once daily
How Supplied	28-count bottles
Storage	Store below 30 ˚C (86 ºF).

Reference ID: 3896186

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On February 25, 2016, we searched the L:drive and AIMS using the terms, Sovaldi to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 2 previous reviews[1,2], and we confirmed our previous recommendations were implemented.

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

[1] Calderon M. 915 Review for Sovaldi (NDA). 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); 2016 February 3. 32 p. OSE RCM No.: 2015-16643.

[2] Calderon M. Post marketing Medication Error Review for Sovaldi (NDA). 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 May 30. 32 p. OSE RCM No.: 2014-857.

Reference ID: 3896186

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/s/

MONICA M CALDERON
03/03/2016

BRENDA V BORDERS-HEMPHILL
03/03/2016

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

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

Application: NDA 208341

Application Type: New NDA

Drug Name(s)/Dosage Form(s): sofosbuvir/velpatasvir fixed dose combination tablet, 400 mg/ 100 mg

Applicant: Gilead Sciences, Inc.

Receipt Date: October 28, 2015

Goal Date: June 28, 2016

1. Regulatory History and Applicant's Main Proposals

Gilead Sciences, Inc (Gilead) submitted an original new drug application (NDA) for sofosbuvir (SOF, GS7977) and velpatasvir (VEL, GS-5816) together as a fixed-dose combination (FDC) tablet, 400 mg/ 100 mg for the treatment of hepatitis C virus (HCV) infection in adults.

Velpatasvir is an HCV NS5A inhibitor that has demonstrated antiviral activity against HCV genotypes 1-6. 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.

SOF/VEL fixed dosed combination was granted Fast Track, and Rolling Review Designations on September 30, 2013, July 22, 2015.

The Division of Antiviral Products granted Breakthrough Therapy (BT) Designation for the SOF/VEL FDC on April 22, 2014. The SOF/VEL FDC for the treatment of chronic hepatitis C virus in genotype , 1, 3, 4, 5, and 6 treatment-naïve patients. On February 4, 2015, Gilead received Intent to rescind letter from the DAVP for the SOF/VEL FDC because the criteria for BT designation was no longer met for the treatment of HCV infection in genotype 1 treatment naïve patients. Breakthrough therapy designation for SOF/VEL FDC tablets remained for the treatment of HCV infection in treatment naïve patients with genotypes 3, 4, 5, and 6. Gilead was provided with an amended BT designation letter on May 15, 2015.

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 of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-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 for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

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

Comment:

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

Comment:

YES 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

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

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. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required

Reference ID: 3864859

Selected Requirements of Prescribing Information

• **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 five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

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

Comment:

Product Title in Highlights

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

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval 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 title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term

Reference ID: 3864859

"**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title 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 must be placed immediately beneath the BW title, and should be centered 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 title 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 five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the 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) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Reference ID: 3864859

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 21. 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 which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. 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 (or will have)** 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 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Reference ID: 3864859

Contents: Table of Contents (TOC)

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

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. 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:

YES 26. The same title 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 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. 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 (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Reference ID: 3864859

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. 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 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 32. 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)]*."

Comment:

Reference ID: 3864859

Selected Requirements of Prescribing Information

YES 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

YES 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

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

Comment:

YES 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), 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:

Reference ID: 3864859

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) 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:

Reference ID: 3864859

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

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

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

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

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Subsection Title
2.2 Subsection Title
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Subsection Title
5.2 Subsection Title
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Immunogenicity
6.2 or 6.3 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Subsection Title
7.2 Subsection Title
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Subpopulation X
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 Subsection Title
14.2 Subsection Title
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

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

37 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

LINDA C ONAGA
12/23/2015

KAREN D WINESTOCK
12/23/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 208341 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: To Be Determined Established/Proper Name: sofosbuvir/velpatasvir Dosage Form: tablets Strengths: 400 mg/100 mg		
Applicant: Gilead Sciences, Inc. Agent for Applicant (if applicable):		
Date of Application: October 28, 2015 Date of Receipt: October 28, 2015 Date clock started after UN:		
PDUFA/BsUFA Goal Date: June 28, 2016	Action Goal Date (if different):	
Filing Date: December 27, 2015	Date of Filing Meeting: November 24, 2015	
Chemical Classification (original NDAs only) : ☒ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): treatment of chronic hepatitis C virus (HCV) infection in adults		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	

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Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☒ Fast Track Designation ☒ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 106739, 118605, 115670	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***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***	☒	☐		

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system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☒		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***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.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov)*: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
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.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted	☐	☒		

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questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• 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)].**	☐	☐		
• 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)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
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)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☒	☐	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: 5 years ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	

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NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
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)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***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.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☒ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	Next Generation Sequencing data received via external hard drive in non CTD 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).	☒	☐	☐	NSG data is not eCTD compatible
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
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:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

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☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
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)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
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)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

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If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***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…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2]	☒	☐		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/uc

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***Note**: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)[3]***	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	Submitted October 30, 2015
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format?	☒	☐		

m027829 htm

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837 htm

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If no, request applicant to submit SPL before the filing date.				
Is the PI submitted in PLR format?[4]	☒	☐		
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? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5] Has a review of the available pregnancy and lactation data been included?	☒ ☒	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted?	☐	☐		

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

[5] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

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If no, request in 74-day letter.				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** June 5, 2014 ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** May 26, 2015 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐			

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ATTACHMENT

MEMO OF FILING MEETING

DATE: November 24, 2015

BACKGROUND:

Gilead Sciences, Inc. (Gilead) submitted an original new drug application (NDA) for sofosbuvir (SOF, GS7977) and velpatasvir (VEL, GS-5816) together as a fixed-dose combination (FDC) tablet, 400 mg/100 mg for the treatment of hepatitis C virus (HCV) infection in adults.

Velpatasvir is an HCV NS5A inhibitor that has demonstrated antiviral activity against HCV genotypes 1-6. 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.

SOF/VEL fixed dosed combination was granted Fast Track and Rolling Review Designations on September 30, 2013, July 22, 2015.

The Division of Antiviral Products granted Breakthrough Therapy (BT) Designation for the SOF/VEL FDC on April 22, 2014. The SOF/VEL FDC for the treatment of chronic hepatitis C virus in genotype , 1, 3, 4, 5, and 6 treatment-naïve patients. On February 4, 2015, Gilead received Intent to rescind letter from the DAVP for the SOF/VEL FDC because the criteria for BT designation was no longer met for the treatment of HCV infection in genotype 1 treatment naïve patients. Breakthrough therapy designation for SOF/VEL FDC tablets remained for the treatment of HCV infection in treatment naïve patients with genotypes 3, 4, 5, and 6. Gilead was provided with an amended BT designation letter on May 15, 2015.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Linda C Onaga	Y
	CPMS/TL:	Karen Winestock	Y
Cross-Discipline Team Leader (CDTL)	Kim Struble		Y
Division Director/Deputy	Debra Birnkrant Jeff Murray		Y
Office Director/Deputy	John Farley		Y

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Clinical	Reviewer:	Prabha Viswanathan Sarah Connelly	Y
	TL:	Kim Struble	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Lisa Naeger Eric Donaldson	Y
	TL:	Jules O'Rear	Y
Clinical Pharmacology	Reviewer:	Jenny Zheng	Y
	TL:	Shirley Seo	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:	Fang Li	Y
	TL:	Jeff Florian	Y
Biostatistics	Reviewer:	Karen Qi	Y
	TL:	Thamban Valappi	Y

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Nonclinical (Pharmacology/Toxicology)	Reviewer:	John Dubinion	Y
	TL:	Hanan Ghantous	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Steve Miller	Y
	RBPM:	Florence Aisida	N
• Drug Substance	Reviewer:	Sithamalli Chandramouli	N
• Drug Product	Reviewer:	George Lunn	Y
• Process	Reviewer:	Ying Wang	N
• Microbiology	Reviewer:		
• Facility	Reviewer:	Christina Capacci-Daniel	N
• Biopharmaceutics	Reviewer:	Ge Bai	N
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Kemi Asante	Y
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Monica Calderon	
	TL:	Vicky Borders-Hemphill	
OSE/DRISK (REMS)	Reviewer:	Erin Hachey	
	TL:	Jamie Wilkins Parker	
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

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Bioresearch Monitoring (OSI)	Reviewer:	Antoine El Hage	N
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Discipline	Reviewer:		
	TL:		
Other attendees			
	*		

FILING MEETING DISCUSSION:

GENERAL • 505 b)(2) filing issues: ○ 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., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

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CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***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***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: ***the application did not raise significant safety or efficacy issues***
• 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? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

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CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	☒ YES ☐ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Reference ID: 3864855

<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☐ YES ☒ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

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REGULATORY PROJECT MANAGEMENT
Signatory Authority: John Farley, MD Deputy Director, OAP **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): February 11, 2016 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☐ Standard Review ☒ Priority Review

	ACTION ITEMS
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	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.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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

/s/

LINDA C ONAGA
12/23/2015

KAREN D WINESTOCK
12/23/2015