

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212477Orig1s000

OTHER REVIEW(S)

Division of Antiviral Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 205834/S-29, tablets (SDN 835)
NDA 212477, oral pellets (SDN 1)

Name of Drug: HARVONI[®] (ledipasvir/sofosbuvir) tablet, 90 mg/400 mg, 45 mg/200 mg
HARVONI[®] (ledipasvir/sofosbuvir) oral pellets, 45 mg/200 mg,
33.75 mg/150 mg

Applicant: Gilead Sciences, Inc.

Labeling Reviewed

Labeling Item: August 12, 2019, US Package Insert (USPI)

Submission Date and Receipt Date: February 28, 2019

Amendments: March 18, 2019; July 10, 2019; August 12, 2019

Reviewed Items: The proposed labeling submitted by the applicant on August 12, 2019, was compared to the last approved labeling dated November 9, 2017 (NDA 205834/S-24).

Background:

Harvoni is a fixed dose combination of ledipasvir, a hepatitis C virus (HCV) NS5A inhibitor and sofosbuvir, a nucleotide analog HCV NS5B polymerase inhibitor. The FDA approved Harvoni on October 10, 2014 and is currently marketed as an oral tablet (ledipasvir and sofosbuvir), 90 mg/ 400 mg for the treatment of chronic HCV infection in patients 12 years of age and older with genotypes 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis.

PREA post-marketing requirements were issued during the initial approval of Harvoni under NDA 205834, and in subsequent prior approval supplements approved on, November 12, 2015 (supplement 3, 5, and 6). The PMRs required Gilead to conduct a pediatric study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of ledipasvir/sofosbuvir in pediatric subjects 3 to 17 years of age with chronic hepatitis C, PREA PMRs requirements 2780-1, 2983-1, and 2985-1.

On February 8, 2014, Gilead submitted a Proposed Pediatric Study Request (PPSR) to the Agency and the Division concluded a Written Request was appropriate. A Written Request was issued September 2, 2016, and revised on December 1, 2016, January 30, 2017, and February 10, 2017. Amendment 3 of the Written Request asked the Sponsor to conduct studies to assess the following:

1. Multiple dose pharmacokinetics (PK) of SOF, GS-331007, and LDV in pediatric patients with chronic HCV infection with genotypes 1, 4, 5 or 6, and compensated liver disease.
2. Safety and effectiveness (SVR12 rate) of LDV/SOF in pediatric patients with chronic HCV infection with genotype 1, 4, 5 or 6 and compensated liver disease.

Gilead submitted Supplement 17 on October 7, 2016, to expand the patient population to include the treatment of pediatric patients 12 years of age and older and weighing at least 35 kg with chronic hepatitis C virus genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis based upon the data from Trial GS-US-334-1116. On October 12, 2016, the Office of Orphan Product Development granted Gilead orphan designation for HARVONI for the treatment of chronic hepatitis C virus (HCV) infection in pediatric patients 3 to less than 18 years of age. Upon approval of the Harvoni sNDA for pediatric patients 12 to less than 18 years of age, Gilead was granted Orphan exclusivity on April 7, 2017 for the treatment of pediatric patients 12 years of age and older or weighing at least 35kg with chronic HCV genotype 1, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis.

On February 28, 2019, the Applicant submitted an original NDA (NDA 212477) and a prior approval supplement (S-29) to NDA 205834. The data from the clinical trial GS-US-337-1116, entitled “A Phase 2, Open-Label, Multicenter, Multi-cohort Study to Investigate the Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed Dose Combination +/- Ribavirin in Adolescents and Children with Chronic HCV-Infection” was submitted to support the fulfillment of the PREA PMRs and Written Request issued to the Harvoni NDA (NDA 205834).

NDA 212477 will have data on the new dosage form and strength of Harvoni, oral pellets, 45 mg/200mg and 33.75mg/150 mg. NDA 205834/S- 29 will add a new dosage strength of Harvoni tablet 45 mg/ 200 mg.

These original NDA and supplement proposes to update the USPI and Patient Information with:

- Information on dosing, administration, storage, and descriptions of the new 45 mg/ 200 mg tablet; 45 mg/ 200 mg and 33.75 mg/ 150, oral pellet
- Data to support the use of HARVONI for patients 3 years of age and older
- Update the Patient Information with corresponding information

The Division accepted the proposed changes with additional proposed modifications outlined below in the review.

Key changes made within the USPI will be detailed in this review. For more additional details and information, reference the attached labeling and discipline reviews.

Review

1. GENERAL

- Minor editorial changes were made throughout the label (i.e. spacing, grammar and capitalization).
- Table numbers, subsections and their references were renumbered throughout as additional tables and subsections were added to the label in this supplement.

2. HIGHLIGHTS OF PRESCRIBING INFORMATION

- HARVONI® (ledipasvir and sofosbuvir) oral pellets formulation was added
- The date was revised from 11/2018 to 8/2019 to reflect the present approval month and year

RECENT MAJOR CHANGES

- This section was updated to reflect the following modifications to the label sections:
 - Removed Boxed Warning 02/2017 and Warnings and Precautions (2.1) 02/2017 since this information has been in the label for more than one year
 - Updated Indications and Usage (1) to update to the month and year of the action
 - Updated Dosage and Administration,
 - Recommended Treatment Regimen and Duration in Patients 3 Years of Age and Older with Genotype 1, 4, 5, or 6 HCV (2.2) 8/2019
 - Recommended Dosage in Pediatric Patients 3 Years of Age and Older (2.4) 8/2019
 - Added Preparation and Administration of Oral Pellets (2.5) 8/2019

INDICATIONS AND USAGE

- Revised indication statement to add “Adults and pediatric patients 3 years of age and older” and adults removed from the bulleted items
- The bulleted item referencing pediatric patients 12 years of age and older removed

DOSAGE AND ADMINISTRATION

- Recommended treatment regimen and duration information updated to include patients 3 years and older
- Consolidated tables containing regimen and duration information for adult patients and for pediatrics into one table
- Recommended dosage information updated to include patients ages 3 years of and older, and referencing the weight-based dosing Table 2, *Dosing for Pediatric Patients 3 Years and Older Using HARVONI Tablets or Oral Pellets*
- Removed bullet item for recommended adult treatment regimen and duration

DOSAGE FORMS AND STRENGTHS

- Added Harvoni tablet strength of 45 mg of ledipasvir and 200 mg of sofosbuvir
- Added Harvoni oral pellets strengths of 45 mg of ledipasvir and 200 mg of sofosbuvir; and 33.75 mg of ledipasvir and 150 mg of sofosbuvir

3. FULL PRESCRIBING INFORMATION: CONTENTS*

- Added subsection, *2.2 Recommended Treatment Regimen and Duration in Patients 3 Years of Age and Older with Genotype 1, 4, 5, or 6 HCV*
- Revised subsection header 2.3 to recommended dosage in adults
- Revised subsection header 2.4 to include patients ages 3 years of age and removed weight requirement of at least 35 kg
- Added subsection, *2.5 Preparation and Administration of Oral Pellets*

4. FULL PRESCRIBING INFORMATION

The following substantive changes were made to the Full Prescribing Information of the labeling:

1 INDICATIONS AND USAGE

- Adult Patients, heading removed to include pediatric patients 3 years and older
- Removed Pediatric Patients indication information

2 DOSAGE AND ADMINISTRATION

- Revised subsection *2.2, Recommended Treatment Regimen and Duration in Patients 3 Years of Age and Older with Genotype 1, 4, 5, or 6 HCV*
 - This new subsection was included to add information on the treatment and duration of HARVONI to include patients 3 years of age and older
 - Table 1, Recommended Treatment Regimen and Duration for HARVONI in Patients 3 Years of Age and Older with Genotype 1, 4, 5, or 6 HCV, for dosing information, was revised to include patients 3 years of age and older
- *2.3 Recommended Dosage in Adults*
 - Language revised to include HCV genotypes 1, 4, 5 or 6
- Added subsection *2.4, Recommended Dosage in Pediatric Patients 3 Years of Age and Older*
 - Added information on the dosing of HARVONI to include patients 3 years of age and older
 - Removed the original Table 2 titled, Recommended Regimen and Duration for HARVONI in Pediatric Patients 12 Years of Age or Older or Weighing at Least 35 kg with Genotype 1, 4, 5, or 6 HCV without Cirrhosis or with Compensated Cirrhosis, as the information is contained in Table 1.

- Revised Table 2 as, Dosing for Pediatric Patients 3 Years and Older Using HARVONI Tablets or Oral Pellets, to add dosing information on the use of HARVONI tablets and oral pellets based on body weight
- Added Table 3, Recommended Dosing for Ribavirin in Combination Therapy with HARVONI for Pediatric Patients 3 Years and Older
- Subsection 2.5, *Preparation and Administration of Oral Pellets*
 - Added information on the preparation of HARVONI oral pellets regarding food and directions for administration

3 DOSAGE FORMS AND STRENGTHS

- Added description of Harvoni tablet strength of 45 mg of ledipasvir and 200 mg of sofosbuvir, including shape, size, and number markers
- Added descriptions of Harvoni oral pellets strengths of 45 mg of ledipasvir and 200 mg of sofosbuvir; and 33.75 mg of ledipasvir and 150 mg of sofosbuvir, including shape, size, and number markers

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

- Adverse Reactions in Pediatric Subjects 3 Years of Age and Older section updated to include number of subjects for patients 3 years and older

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

- Included HCV genotype 4 regarding data for treatment-naïve and treatment-experienced pediatric patients from Study 1116
- Updated the numbering of study participants from Study 1116 and included pediatric patients 3 years and older
- Updated the established safety and efficacy statement of Harvoni with the removal of “less than 35 kg” and modification of the age to less than 3 years of age in pediatric patients from the previous 12 years of age
- Added information on rationale to support dosing recommendation for pediatric patients with genotype 1 HCV with decompensated cirrhosis and/or pediatric patients, genotypes 1 and 4, who are liver transplant recipients with cirrhosis or without compensated cirrhosis
- Updated the established safety and efficacy statement of Harvoni to only pediatric patients less than 3 years of age, including removing the “weighing less than 35 kg, in pediatric patients with decompensated cirrhosis, or in pediatric liver transplant recipients” language

11 DESCRIPTION

- Added the ingredients of the tablet and film-coating material from the 45 mg of ledipasvir and 200 mg sofosbuvir tablets

- Added the ingredients of the oral pellet containing either 45 mg ledipasvir and 200 mg sofosbuvir or 33.75 mg ledipasvir and 150 mg sofosbuvir, contained in packets

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

- Pediatric Patients subsection updated to include HCV genotypes 1, 3, or 4 infected pediatric subjects 3 years of age and older
- Table 7, Pharmacokinetic Properties of the Components of HARVONI in HCV-Infected Pediatric Subjects 3 Years of Age and Older, modified to include information on dosing, PK Parameters as geometric means categorized by weight groups less than 17 kg, 17 to less than 35 kg, and greater than or equal to 35 kg
- Added GS-331007 as unestablished pharmacokinetics with patients to less than 3 years, updated from less than 12 years of age

12.4 Microbiology

- Effect of Baseline HCV Polymorphisms on Treatment Response
 - Pediatrics subsection was updated to reflect additional pediatric data for reported numbers of resistance-associated polymorphism

14 CLINICAL STUDIES

14.1 Description of Clinical Trials

- Genotype 4 added, and age updated to 3 years of age and older to reflect new data from Study 1116
- Table 10, Trials Conducted with HARVONI with or without Ribavirin in Subjects with Chronic HCV Genotype 1, 4, 5, or 6 Infection
 - Trial 1116 updated to reflect ages 3 years of age and older, and referencing genotype 4 and treatment duration of HARVONI for 24 weeks to reflect one new subject
 - Number of patients updated to 223 from 100 from new Study 1116 data

14.6 Clinical Trial in Pediatric Subjects

- Information from Study 1116 added to this section, lowered the age of pediatric patients to 3 years old and including information on the dose and duration of treatment studied
- Additional information on the SVR12 from Study 1116 added on to patients 6 years to less than 12 years and patients 3 years to less than 6 years of age

16 HOW SUPPLIED/STORAGE AND HANDLING

- Added description of HARVONI tablets
- Storage of tablets revised to “below 30 °C (86 °F) for consistency with the carton labeling
- Added description, storage, and handling information of HARVONI oral pellets

17 PATIENT COUNSELING INFORMATION

- ATRIPLA added as trademark of Gilead and removing reference of Bristol Myers Squibb

5. Patient Information

- Added HARVONI® oral pellets
- Revised date to 08/2019

What is HARVONI?

- Added children 3 years of age and older
- Removed language regarding the treatment of children 12 years of age and older and weighing at least 77 pounds

How should I take HARVONI?

- Revised to include pellets and dose strength tablet
- Provided directions for children 3 years of age and older
- Added warning about missing a dose of HARVONI

How should I give HARVONI oral pellets to my child?

- This section was added to provide caregivers directions on how to administer HARVONI oral pellets to children 3 years and older

How should I store HARVONI?

- Removed “at room temperature” to match the carton labeling storage requirements
- Added warning about the use of HARVONI oral pellets and tamper-evident seals

What are the ingredients in HARVONI?

- Added ingredient information for HARVONI oral pellets and tablets 45 mg /200 mg

Recommendations

Based upon the changes highlighted in this review and the reviews from the clinical pharmacology and clinical disciplines, this original NDA and this supplement should be approved. Please see the individual reviews for additional information.

Philip Villasurda

Regulatory Project Manager

Date

Karen Winestock

Chief, Project Management Staff

Date

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/s/

PHILIP R VILLASURDA
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Signing of behalf of Karen Winestock, CPMS

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

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

Memorandum

Date: 8/15/19

To: Philip Villasurda
Regulatory Project Manager
Division of Antiviral Products (DAVP)

From: Nima Ossareh, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for HARVONI® (ledipasvir and sofosbuvir) tablets, for oral use, HARVONI® (ledipasvir and sofosbuvir) oral granules, SOVALDI® (sofosbuvir) tablets, for oral use, and SOVALDI® (sofosbuvir) oral granules

NDA/BLA: 205834/Supplement 29 and 212477 204671 Supplement 14

In response to DAVP consult request dated March 19, 2019, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for HARVONI® (ledipasvir and sofosbuvir) tablets, for oral use, HARVONI® (ledipasvir and sofosbuvir) oral granules, SOVALDI® (sofosbuvir) tablets, for oral use, and SOVALDI® (sofosbuvir) oral granules. These supplements revise the label to provide information on the efficacy in patients 3 years of age and older.

PI: OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from Division of Antiviral Products (DAVP) on August 12, 2019 and are provided below.

PPI: A combined OPDP and Division of Medical Policy Programs (DMPP) review of the PPI will be completed under a separate cover.

Thank you for your consult. If you have any questions, please contact Nima Ossareh at (240) 402-2769 or nima.ossareh@fda.hhs.gov.

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

PATIENT LABELING REVIEW

Date: August 13, 2019

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)

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

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

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

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

Dosage Form and Route: oral granules

Application Type/Number/Supplement Number: NDA 212477 and NDA 205834/S-029

Applicant: Gilead Sciences, Inc.

1 INTRODUCTION

On February 28, 2019, Gilead Sciences, Inc. submitted for the Agency's review an original New Drug Application (NDA) 212477 for HARVONI (ledipasvir and sofosbuvir) oral granules. This original NDA references NDA 205834/S-029 HARVONI (ledipasvir and sofosbuvir) tablets. This application is intended to support the approval to market HARVONI (ledipasvir and sofosbuvir) oral granules for use in the treatment of hepatitis C virus (HCV) infection in pediatric patients.

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 March 19, 2019 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for HARVONI (ledipasvir and sofosbuvir) oral granules.

2 MATERIAL REVIEWED

- Draft HARVONI (ledipasvir and sofosbuvir) oral granules PPI received on February 28, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 2, 2019.
- Draft HARVONI (ledipasvir and sofosbuvir) oral granules Prescribing Information (PI) received on February 28, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 2, 2019.

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.

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

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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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: July 15, 2019
Requesting Office or Division: Division of Antiviral Products (DAVP)
Application Type and Number: NDA 212477
Product Name and Strength: Harvoni (ledipasvir and sofosbuvir) Oral Pellets,
45 mg/200 mg; 33.75 mg/150 mg
Applicant/Sponsor Name: Gilead Sciences, Inc.
FDA Received Date: July 10, 2019
OSE RCM #: 2019-471-1
DMEPA Safety Evaluator: Valerie S. Wilson, PharmD
DMEPA Team Leader: Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on July 10, 2019 for Harvoni . The Division of Antiviral Products (DAVP) requested that we review the revised labels and labeling for Harvoni (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our previous recommendations. However, we note the applicant's use of oral granules to describe this product's dosage form. We defer to the Office of Pharmaceutical Quality (OPQ) to determine the appropriate dosage form for this product and recommend the carton and container labels are updated accordingly to prevent confusion.

^a Wilson, V. Label and Labeling Review for Harvoni (NDA 212477). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUN 21. RCM No.: 2019-471.

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/s/

SEVAN H KOLEJIAN on behalf of VALERIE S WILSON
07/15/2019 03:28:57 PM

SEVAN H KOLEJIAN
07/15/2019 03:30:29 PM

LABEL, LABELING, AND PACKAGING 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:	June 21, 2019
Requesting Office or Division:	Division of Antiviral Products (DAVP)
Application Type and Number:	NDA 205834/S-029 and NDA 212477
Product Name and Strength:	Harvoni (ledipasvir and sofosbuvir), Tablets: 90 mg/400 mg; 45 mg/200 mg Oral Pellets: 45 mg/200 mg; 33.75 mg/150 mg
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Gilead Sciences, Inc
FDA Received Date:	February 28, 2019 and March 18, 2019
OSE RCM #:	2019-482 and 2019-471
DMEPA Safety Evaluator:	Valerie S. Wilson, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 REASON FOR REVIEW

Gilead submitted an efficacy supplement for Harvoni (ledipasvir and sofosbuvir) tablets (NDA 205834/S-029) to support expansion of the patient population and the addition of a new strength of Harvoni tablets (45 mg/200 mg). Additionally, Gilead submitted New Drug Application (NDA) 212477 to support the addition of Harvoni oral pellets, 45 mg/200 mg and 33.75 mg/150 mg, to the Harvoni product line. Subsequently, the Division of Antiviral Products requested that we review the proposed labels and labeling for areas that may lead to medication errors.

These applications are intended to share a single U.S. Prescribing Information. Thus, this review includes our combined assessment of both NDA 205834/S-029 and NDA 212477.

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
Human Factors Study	C (N/A)
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

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

			<i>specific dosing guidelines based on body weight. (2.3)”</i>
Full Prescribing Information			
1.	Section 2.3 includes examples of non-acidic foods in which Harvoni oral pellets can be administered but does not include examples of non-acidic liquids in which Harvoni oral pellets can be administered. We are concerned that this could lead to administration errors.	Section 2.3 indicates that Harvoni oral pellets is to be administered with non-acidic soft food (b) (4). Common household beverages include acidic liquids such as orange juice or soda and end users could inadvertently administer Harvoni oral pellets with an acidic liquid. Additionally, our Office of Pharmaceutical Quality colleagues believe acidic foods and liquids may affect (b) (4).	To provide clarity, we recommend including at least 3 examples of non-acidic liquids for which prescribers can use as guidance when instructing patients and caregivers on the proper administration of Harvoni oral pellets. Additionally, for consistency, we recommend the same non-acidic liquid examples be included in the <i>How should I give HARVONI oral pellets to my child?</i> section of the Patient Package Insert.

Table 3: Identified Issues and Recommendations for Gilead Sciences, Inc. (entire table to be conveyed to Applicant)

Container Labels, Carton Labeling, and Packaging			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	The quantity statement on the cartons for Harvoni oral pellets includes the phrase “(b) (4),” which could result in administration errors.	The use of the phrase “(b) (4)” is inconsistent with the Harvoni oral pellets 90 mg/400 mg dosage regimen that requires administration of two 45 mg/200 mg packets of pellets once daily.	Revise the quantity statement to read: “28 packets”.
3.	The format of the expiration date is not defined on the container	We are unable to evaluate whether the proposed format of the expiration reduces the risk of	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration

	labels and carton labeling.	deteriorated drug medication errors.	<p>date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.</p> <p>See <i>Draft Guidance: Product Identifiers Under the Drug Supply Chain Security Act- Questions and Answers, September 2018 (lines 277-283)</i> for further insight into FDA's current thinking (found at: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf)</p>
4.	The product identifier required under the Drug Supply Chain Security Act (DSCSA) is missing from the container labels of	DSCSA requires certain prescription drugs to have a human-readable and machine-readable (2D data matrix barcode) product	Ensure applicable container labels and carton labeling for Harvoni meet the product identifier requirements of the

	Harvoni tablets and the carton labeling of Harvoni oral pellets.	identifier on the smallest saleable unit for tracking and tracing purposes. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. ^a The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively.	Drug Supply Chain Security Act.
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4 CONCLUSION

Our evaluation of the proposed prescribing information, container labels, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to the applicant so that recommendations are implemented prior to approval of NDA 205834/S-29 and NDA 212477.

^a The draft guidance is available from: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Harvoni received on March 18, 2019 from Gilead Sciences, Inc.

Table 2. Relevant Product Information for Harvoni	
Initial Approval Date	Tablets: October 10, 2014 Oral Pellets: N/A
Active Ingredient	ledipasvir and sofosbuvir
Indication	<p><u>Adult Patients:</u> Treatment of adult patients with chronic hepatitis C virus (HCV):</p> <ul style="list-style-type: none"> • Genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis • Genotype 1 infection with decompensated cirrhosis, for use in combination with ribavirin • Genotype 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis, for use in combination with ribavirin <p style="text-align: right;">(b) (4)</p> <p style="color: red;">(proposed)</p>
Route of Administration	Oral
Dosage Form	Tablets Oral Pellets
Strength	Tablets: 90 mg/400 mg; 45 mg/200 mg Oral Pellets: 45 mg/200 mg; 33.75 mg/150 mg
Dose and Frequency	<p>Recommended Dosage in Adults</p> <ul style="list-style-type: none"> • One tablet (90 mg ledipasvir and 400 mg sofosbuvir) once daily <p>Recommended Dosage in Pediatric Patients 3 Years of Age or Older</p> <ul style="list-style-type: none"> • (b) (4) • (b) (4)

	<p>Table 2 Dosing for Pediatric Patients 3 Years (b) (4) Using HARVONI Tablets or Oral Granules</p> <table border="1"> <thead> <tr> <th>Body Weight (kg)</th> <th>Dosing of HARVONI Tablets or Oral Granules</th> <th>Ledipasvir/Sofosbuvir Daily Dose</th> </tr> </thead> <tbody> <tr> <td>at least 35</td> <td>one 90/400 mg tablet once daily or two 45/200 mg tablets once daily or two 45/200 mg packets of granules once daily</td> <td>90/400 mg/day</td> </tr> <tr> <td>17 to less than 35</td> <td>one 45/200 mg tablet once daily or one 45/200 mg packet of granules once daily</td> <td>45/200 mg/day</td> </tr> <tr> <td>less than 17</td> <td>one 33.75/150 mg packet of granules once daily</td> <td>33.75/150 mg/day</td> </tr> </tbody> </table> <p>(b) (4) Do not chew HARVONI granules. If HARVONI granules are administered with food, sprinkle the granules on one or more spoonfuls of non-acidic soft food (b) (4) at or below room temperature. Examples of non-acidic foods include pudding, chocolate syrup, mashed potato, and ice cream. Take HARVONI granules within 30 minutes of gently mixing with food and swallow the entire contents without chewing to avoid a bitter aftertaste.</p>	Body Weight (kg)	Dosing of HARVONI Tablets or Oral Granules	Ledipasvir/Sofosbuvir Daily Dose	at least 35	one 90/400 mg tablet once daily or two 45/200 mg tablets once daily or two 45/200 mg packets of granules once daily	90/400 mg/day	17 to less than 35	one 45/200 mg tablet once daily or one 45/200 mg packet of granules once daily	45/200 mg/day	less than 17	one 33.75/150 mg packet of granules once daily	33.75/150 mg/day
Body Weight (kg)	Dosing of HARVONI Tablets or Oral Granules	Ledipasvir/Sofosbuvir Daily Dose											
at least 35	one 90/400 mg tablet once daily or two 45/200 mg tablets once daily or two 45/200 mg packets of granules once daily	90/400 mg/day											
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less than 17	one 33.75/150 mg packet of granules once daily	33.75/150 mg/day											
How Supplied	<p>Tablets: bottles of 28 tablets with silica gel desiccant and polyester coil Oral Pellets: cartons containing 28 packets</p>												
Storage	<p>Tablets</p> <ul style="list-style-type: none"> Store at room temperature below 30 °C (86 °F). Dispense only in original container. <p>Oral Pellets</p> <ul style="list-style-type: none"> Store at room temperature below 30 °C (86 °F). Do not use if carton tamper-evident seal or packet seal is broken or damaged. 												
Container Closure	<p>Tablets:</p> <p><u>90 mg/400 mg</u></p> <ul style="list-style-type: none"> 100 mL, white, high density polyethylene (HDPE) bottle and a (b) (4) child-resistant cap (b) (4) <p><u>45 mg/200 mg</u></p> <ul style="list-style-type: none"> 45 mL, white, high density polyethylene (HDPE) bottle and a (b) (4) child-resistant cap (b) (4) <p>Oral Pellets:</p> <ul style="list-style-type: none"> (b) (4) 												

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 24, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, Harvoni and NDA 205834. Our search identified seven previous reviews^{b,c,d,e,f,g,h} and we confirmed that our previous recommendations were implemented.

^b Wilson, V. Labeling Review for Harvoni (NDA 205834). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 FEB 03. RCM No.: 2016-2585.

^c Calderon, M. Label and Labeling Review for Harvoni (NDA 205834). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 NOV 5. RCM No.: 2015-2025.

^d Calderón, M. Label, Labeling, and Packaging Review for Harvoni (NDA 205834). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 OCT 7. RCM No.: 2015-1105-1

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

^f Calderón, M. Medication Error Postmarket Review for Harvoni (NDA 205834). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 AUG 19. RCM No.: 2015-1105

^g Calderon, M. Label and Labeling Review Memo for Harvoni (NDA 205834). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 AUG 21. RCM No.: 2014-353-1.

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

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On April 24, 2019, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care ISMP Medication Safety Alert Community/Ambulatory Care ISMP Medication Safety Alert Nurse Advise-ERR Long-Term Care Advise-ERR ISMP Canada Safety Bulletin Pennsylvania Patient Safety Advisory
Search Strategy and Terms	Match Exact Word or Phrase: Harvoni

D.2 Results

The search retrieved no relevant articles associated with label and labeling for Harvoni.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

On April 24, 2019, we searched FAERS using the criteria in the table below and identified 30 cases. We individually reviewed the cases, and limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.ⁱ We excluded 30 cases because they described dose omission/missed dose (n=22); accidental overdose (n=2); therapeutic duration too short (n=1); Harvoni tablets dispensed outside original container (n=1); insufficient information to determine if a medication error occurred (n=4).

Criteria Used to Search FAERS	
Initial FDA Receive Dates:	December 1, 2018 to March 30, 2019
Product Name:	Harvoni
Product Active Ingredient (PAI):	
Event:	<i>SMQ Medication errors (Narrow)</i>
Country (Derived):	USA

E.2 Results

Our search did not identify any cases, relevant for this review.

E.3 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

ⁱ The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

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

- Container label received on February 28, 2019
 - Harvoni Tablets, 45 mg/200 mg
 - Harvoni Tablets, 90 mg/400 mg – current in use container label
 - Harvoni Oral Pellets, 33.75 mg/150 mg
 - Harvoni Oral Pellets, 45 mg/200 mg
- Carton labeling received on February 28, 2019
 - Harvoni Oral Pellets, 33.75 mg/150 mg
 - Harvoni Oral Pellets, 45 mg/200 mg
- Prescribing Information and Patient Package Insert (Image not shown) received on March 18, 2019. Available at: <\\cdsesub1\evsprod\nda205834\0212\m1\us\114-labeling\draft\labeling\draft-labeling-text-stk.pdf>

G.2 Label and Labeling Images

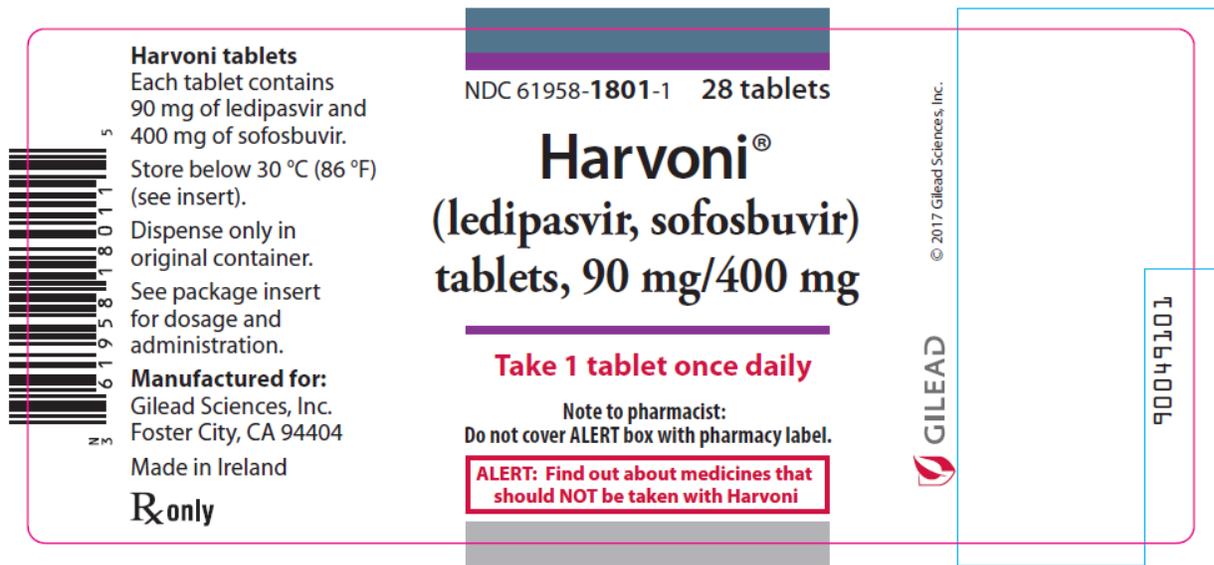
Container Label for Harvoni Tablets, 45 mg/200 mg

(b) (4)



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

Current In-Use Container Label for Harvoni Tablets, 90 mg/400 mg



Harvoni tablets
Each tablet contains
90 mg of ledipasvir and
400 mg of sofosbuvir.
Store below 30 °C (86 °F)
(see insert).
Dispense only in
original container.
See package insert
for dosage and
administration.

Manufactured for:
Gilead Sciences, Inc.
Foster City, CA 94404
Made in Ireland

Rx only

NDC 61958-1801-1 28 tablets

Harvoni[®]
(ledipasvir, sofosbuvir)
tablets, 90 mg/400 mg

Take 1 tablet once daily

Note to pharmacist:
Do not cover ALERT box with pharmacy label.

**ALERT: Find out about medicines that
should NOT be taken with Harvoni**

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90049101

Container Labels for Harvoni Oral Pellets Unit-Dose Packets



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

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

VALERIE S WILSON
06/21/2019 02:48:02 PM

SEVAN H KOLEJIAN
06/21/2019 02:57:02 PM