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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 lease 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.

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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 ADMINISRATION

- 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

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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*

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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.

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