CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
3Q17 July-August

BRAND NAME
Harvoni®

GENERIC NAME
sofosbuvir/ledipasvir

MANUFACTURER
Gilead Sciences, Inc.

DATE OF APPROVAL
April 7, 2017

PRODUCT LAUNCH DATE
Already on the market

REVIEW TYPE

☐ Review type 1 (RT1): New Drug Review
Full review of new chemical or biologic agents

☒ Review type 2 (RT2): New Indication Review
Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use

☐ Review type 3 (RT3): Expedited CMS Protected Class Drug Review
Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastic, antipsychotics, antiretrovirals, and immunosuppressants)

☐ Review type 5 (RT5): Abbreviated Reviews for Intravenous Chemotherapy Agents
Abbreviated review for intravenous chemotherapy agents which are usually covered under the medical benefit

FDA APPROVED INDICATION(S)

Current Indication(s)
For the treatment of chronic hepatitis C virus (HCV) in:
• Adults with genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis
• Adults with genotype 1 infection with decompensated cirrhosis, in combination with ribavirin

• Adults with genotype 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis, in combination with ribavirin

New/Revised Indication(s)
Pediatric patients 12 years of age and older or weighing at least 35 kg with genotype 1, 4, 5, or 6 without cirrhosis or with compensated cirrhosis

OFF-LABEL USES
Not applicable

CLINICAL EFFICACY
The efficacy of Harvoni was evaluated in an open-label trial (Study 1116) that evaluated 12 weeks of treatment with Harvoni once daily in genotype 1 HCV treatment-naïve (N=80) and treatment-experienced (N=20) pediatric subjects 12 years of age and older without cirrhosis or with compensated cirrhosis. The primary efficacy outcome was sustained virologic response 12 weeks after treatment ended (SVR12). Secondary outcomes included safety and tolerability as well as pharmacokinetics relative to adults.

Demographics and baseline characteristics were balanced across treatment-naïve and treatment-experienced subjects (patients had failed an interferon based regimen with or without ribavirin). Of the 100 treated subjects, the median age was 15 years (range: 12 to 17); 63% of the subjects were female; 90% were White, 7% were Black, and 2% were Asian; 13% were Hispanic/Latino; mean body mass index was 23 kg/m2 (range: 13.1 to 36.6 kg/m2); mean weight was 61 kg (range 33 to 126 kg); 55% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; 81% had genotype 1a HCV infection; 76% had non-CC IL28B alleles (CT or TT). One subject had known compensated cirrhosis. The majority of subjects (84%) had been infected through vertical transmission.

The SVR12 rate was 98% overall (98% [78/80] in treatment-naïve subjects and 100% [20/20] in treatment-experienced subjects). No subject experienced on-treatment virologic failure or relapse. Two subjects were lost to follow-up. Overall, there are 71 treatment-emergent adverse reactions (TEAE), with no serious or grade 3 or 4 TEAEs. There were 9 grade 3 or 4 laboratory abnormalities and 1 incidence of hemoglobin <10 g/dL. The most commonly observed TEAEs ($\geq$10%) included: headache, nausea, upper abdominal pain, diarrhea, fatigue, vomiting, cough, oropharyngeal pain. No treatment discontinuations occurred due to adverse events.

CONTRAINDICATIONS
None identified

BLACK BOX WARNINGS
Risk of hepatitis B virus (HBV) reactivation in patients co-infected with HCV and HBV

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DRUG INTERACTIONS

- Coadministration with amiodarone may result in serious symptomatic bradycardia.
- Use of Harvoni with amiodarone is not recommended.
- P-gp inducers (e.g., rifampin, St. John's wort): May alter concentrations of ledipasvir and sofosbuvir. Use of Harvoni with P-gp inducers is not recommended.

ADVERSE REACTIONS

The most common adverse reactions (incidence greater than or equal to 10%, all grades) observed with treatment with Harvoni were fatigue, headache and asthenia.

DOSAGE AND ADMINISTRATION

Pediatric Patient Population 12 Years of Age and Older or Weighing at Least 35 Kg.

- Genotype 1 treatment-naïve without cirrhosis or with compensated cirrhosis (Child-Pugh A): 12 weeks
- Genotype 1 treatment-experienced without cirrhosis: 12 weeks
- Genotype 1 treatment-experienced with compensated cirrhosis (ChildPugh A): 24 weeks
- Genotype 4, 5, or 6 Treatment-naïve and treatment experienced, without cirrhosis or with compensated cirrhosis (Child-Pugh A): 12 weeks

PRODUCT AVAILABILITY

Tablets: 90 mg ledipasvir and 400 mg sofosbuvir

THERAPEUTIC ALTERNATIVES

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Utilization Management Recommendation

- There is significant potential for inappropriate use and utilization management should be considered for the following reason(s):

  i) To prevent inappropriate use of medications that have a significant potential for use that may lead to inferior or unpredictable outcomes.
  (1) Opportunity exists to obtain clinically significant medical or laboratory information necessary to determine appropriate use of the medication.

  (a) FDA indication is specific to genotype, treatment history, and cirrhosis status to identify candidates for treatment for specific duration of therapy.

  ii) Recommended utilization management tool(s): (check all that apply)
  (1) ☒ Prior authorization
  (2) ☐ Quantity limits
  (3) ☐ Provider newsletter
  (4) ☐ Hard block (plan exclusion)
  (5) ☐ Messaging
  (6) ☐ Electronic step therapy

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(7) ☐ Clinical Program
Product Comparison
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REFERENCES:

1. Harvoni Prescribing Information. Foster City, CA: Gilead Sciences, Inc.; April 2017. Available at http://www.harvoni.com/. Accessed April 19, 2017.
2. Wirth S, Gonzalez-Peralta R, Rosenthal P, et al. Sofosbuvir-Containing Regimens are Safe and Effective in Adolescents with Chronic hepatitis C Infection. The 26th Annual Meeting of the Asian pacific Association for the Study of the Liver (APASL) in February 15-19, 2017 in Shanghai, China.
3. Squires JE, Balisteri WF. Hepatitis C Virus Infection in Children and Adolescents. Hepatology Communications 2017; 1(2): 87-98.
4. Guidelines for the screening, care and treatment of persons with hepatitis C infection. World Health Organization April 2016. Available at http://www.who.int/hepatitis/publications/en/. Accessed April 19, 2017.
5. HCV guidance: Recommendations for testing, managing, and treating hepatitis C. AASLD-IDSA April 2017. Available at http://www.hcvguidelines.org. Accessed June 12, 2017.