This drug requires a written request for prior authorization. All requests for hepatitis C medications require review by a pharmacist prior to final approval.

GUIDELINES FOR USE

1. Is the patient at least 18 years old?
   If yes, continue to #2.
   If no, do not approve.
   **DENIAL TEXT:** See the denial text at the end of the guideline.

2. Does the patient have a diagnosis of chronic hepatitis C, with genotype 1, genotype 4, genotype 5, or genotype 6?
   If yes, continue to #3.
   If no, do not approve.
   **DENIAL TEXT:** See the denial text at the end of the guideline.

3. Does the patient have evidence of hepatitis C infection (e.g., at least two detectable HCV RNA levels separated by 6 months), or if patient has acute infection, has the patient received monitoring of HCV RNA for at least 6 months, with at least two detectable HCV RNA levels over the past 6 months (separated by 6 months)?  *(Note: If patient has evidence of prescriptions for past treatment for hepatitis C, one detectable HCV RNA level within the last 6 months is acceptable.)*
   If yes, continue to #4.
   If no, do not approve.
   **DENIAL TEXT:** See the denial text at the end of the guideline.

CONTINUED ON NEXT PAGE
4. Does the patient have evidence of fibrosis stage 3 or 4 as determined by any ONE of the following:
   - Metavir score F3 or F4 from liver biopsy
   - APRI score above 1.5
   - Radiological Imaging consistent with cirrhosis
   - Evidence from physical exam and clinical findings consistent with cirrhosis
   - Fibroscan score of 9.5kPa or higher
   - Fibrotest result of 0.58 or higher

   If yes, continue to #6.
   If no, continue to #5.

5. Does the patient have Metavir Stage 2 with another condition listed as “high priority” or “highest priority” for treatment, such as liver transplant recipient, severe extra-hepatic hepatitis C, other co-existing liver disease such as non-alcoholic steatohepatitis, debilitating fatigue, porphyria cutanea tarda, diabetes type 2, hepatitis B or HIV coinfection? Note: Metavir Stage 2 can be determined by any one of the following:
   - Metavir score F2 from liver biopsy
   - APRI score above 0.78
   - Fibroscan score of 7.65kPa or higher
   - Fibrotest result of 0.5 or higher

   If yes, continue to #6.
   If no, do not approve.

   DENIAL TEXT: See the denial text at the end of the guideline.

6. Does the patient have end stage renal disease or require dialysis?

   If yes, do not approve.
   
   DENIAL TEXT: See the denial text at the end of the guideline.
   If no, continue to #7.

7. Is the patient currently supervised by a gastroenterologist, infectious disease specialist, physician specializing in the treatment of hepatitis (for example, a hepatologist), or a specially trained group such as ECHO (Extension for Community Healthcare Outcomes) model?

   If yes, continue to #8.
   If no, do not approve.

   DENIAL TEXT: See the denial text at the end of the guideline.

CONTINUED ON NEXT PAGE
LEDIPASVIR/SOFOSBUVIR

GUIDELINES FOR USE (CONTINUED)

8. Does the patient have decompensated cirrhosis?
   
   If yes, do not approve.
   DENIAL TEXT: See the denial text at the end of the guideline.
   If no, continue to #9.

9. Is the patient currently taking any of the following medications: amiodarone, carbamazepine, phenytoin, phenobarbital, oxcarbazepine, rifampin, rifabutin, rifapentine, rosuvastatin, simeprevir, sofosbuvir, Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir), or tipranavir/ritonavir?

   If yes, do not approve.
   DENIAL TEXT: See the denial text at the end of the guideline.
   If no, continue to #10.

10. Has the patient been evaluated to be absent of current alcohol and other substance abuse, with 1) validated screening instruments (e.g., AUDIT or AUDIT C) or via physician attestation AND 2) a urine toxicology screen at baseline?

   If yes, continue to #11.
   If no, do not approve.
   DENIAL TEXT: See the denial text at the end of the guideline.

11. Does the patient have a limited life expectancy (less than 12 months) due to non-liver related comorbid conditions (e.g., physician attestation)?

   If yes, do not approve.
   DENIAL TEXT: See the denial text at the end of the guideline.
   If no, continue to #12.

12. Is this request for treatment of genotype 4, 5, or 6?

   If yes, approve for 12 weeks by HICL for #1 tablet per day.
   If no, continue to #13.

13. Is the patient treatment naïve?

   If yes, continue to #14.
   If no, continue to #17.

CONTINUED ON NEXT PAGE
GUIDELINES FOR USE (CONTINUED)

14. Does the patient have cirrhosis?
   
   If yes, **approve for 12 weeks by HICL for #1 tablet per day.**
   If no, continue to #15.

15. Does the patient have pre-treatment HCV RNA level less than 6 million IU/mL?
   
   If yes, continue to #16.
   If no, **approve for 12 weeks by HICL for #1 tablet per day.**

16. Does the patient have HIV coinfection?
   
   If yes, **approve for 12 weeks by HICL for #1 tablet per day.**
   If no, **approve for 8 weeks by HICL for #1 tablet per day.**
   
   **APPROVAL TEXT:** 8 weeks of treatment approved for treatment naïve patients (no cirrhosis) with HCV RNA level less than 6 million IU/mL. Requests for treatment duration longer than 8 weeks will require further information from the healthcare provider.

17. Has the patient received prior treatment (e.g., treatment-experienced patient) for hepatitis C with 1) peginterferon and ribavirin or 2) triple therapy with HCV protease inhibitor, peginterferon and ribavirin?
   
   If yes, continue to #18.
   If no, obtain Medical Director Review.
   
   **DENIAL TEXT:** See the denial text at the end of the guideline.

18. Does the patient have cirrhosis?

   If yes, **approve for 24 weeks by HICL for #1 tablet per day.**
   If no, **approve for 12 weeks by HICL for #1 tablet per day.**

   **CONTINUED ON NEXT PAGE**
DENIAL TEXT: Our guideline for SOFOSBUVIR/LEDIPASVIR requires a diagnosis of hepatitis C. In addition, the following criteria must also be met:

- has genotype 1, genotype 4, genotype 5, or 6 hepatitis C
- patient is at least 18 years old
- is currently supervised by a gastroenterologist, infectious disease specialist, physician specializing in the treatment of hepatitis (for example, a hepatologist), or a specially trained group such as ECHO (Extension for Community Healthcare Outcomes) model
- patient has evidence of fibrosis stage 3 or 4 (Metavir F3 or F4 equivalent) or Metavir F2 with another condition listed as “high priority” or “highest priority” for treatment, such as liver transplant recipient, severe extra-hepatic hepatitis C, other co-existing liver disease such as non-alcoholic steatohepatitis, debilitating fatigue, or porphyria cutanea tarda, diabetes type 2, hepatitis B or HIV coinfection
- documentation of HCV infection (e.g., at least two detectable HCV RNA levels) separated by 6 months (or past prescription for treatment of hepatitis C and at least one detectable HCV RNA level).
- For treatment-experienced patients with genotype 1, previous dual therapy with peginterferon and ribavirin or triple therapy with HCV protease inhibitor, peginterferon and ribavirin is required.

The medication will not be approved for the following patients:

- patient using any of the following medications concurrently while on Harvoni: amiodarone, carbamazepine, phenytoin, phenobarbital, oxcarbazepine, rifampin, rifabutin, rifapentine, rosvastatin, simeprevir, sofosbuvir, Stribild (elvitegravir/cobicistat/emericitabine/ tenofovir), or tipranavir/ritonavir
- patient with decompensated cirrhosis
- patient with end stage renal disease
- patient on dialysis
- patient must be evaluated for (and absent of) current alcohol and other substance abuse with validated screening instruments (e.g., AUDIT or AUDIT C) or physician attestation AND a urine toxicology screen at baseline
- patient with limited life expectancy (less than 12 months) due to non-liver related comorbid conditions.

CONTINUED ON NEXT PAGE
RATIONALE
Ensure appropriate utilization of Harvoni (sofosbuvir/ledipasvir).

FDA APPROVED INDICATIONS
For the treatment of chronic hepatitis C genotype 1 infection in adults

FDA APPROVED DOSAGE
• One 400mg/90mg tablet taken once daily with or without food.

For genotype 1, duration of therapy is as follows:

<table>
<thead>
<tr>
<th>Treatment type</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment naïve, with or without cirrhosis</td>
<td>12 weeks*</td>
</tr>
<tr>
<td>Treatment experienced, without cirrhosis</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Treatment experienced, with cirrhosis</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

* = Treatment of 8 weeks can be considered in treatment naïve patients without cirrhosis who have a pretreatment HCV RNA load of <6 million IU/mL.

Therapy for genotype 4 and 6 is not FDA approved at this time; however, AASLD recommends Harvoni for 12 weeks as an option for genotypes 4 and 6.

OTHER INFORMATION
Harvoni is the first single tablet, all-oral combination therapy approved to treat chronic hepatitis C. It is a combination of sofosbuvir, a NS5B polymerase inhibitor (currently also available as a single ingredient medication under brand Sovaldi), with ledipasvir, a new NS5A inhibitor. Potential advantages for Harvoni include once daily dosing, excellent tolerability, improved SVR rates, and it is the first agent to offer an all-oral, interferon-free treatment option for all genotype 1 patients with treatment duration as short as 8 weeks for certain patients. Because it is the first interferon-free regimen to be FDA-approved to treat all genotype 1 patients, initial demand for this agent is expected to be high. Harvoni joins Sovaldi (sofosbuvir) as well as the NS3/4A protease inhibitors (Olysio (simeprevir), Victrelis (boceprevir), and Incivek (telaprevir)) as the fifth oral, direct-acting antiviral agent for treatment of chronic hepatitis C. Incivek (telaprevir) was previously available but has been recently discontinued by the manufacturer due to low demand. Harvoni differs from these agents in that it does not require additional components in the treatment regimen (e.g., ribavirin and/or peginterferon alfa).

Current treatment guidelines for hepatitis C (December 2014) were updated to include Harvoni as a recommended treatment option for genotype 1, 4, or 6. Please visit the website www.hcvguidelines.org for the most up-to-date recommendations.

CONTINUED ON NEXT PAGE
AASLD/IDSA Guidance for treatment of HCV infection (adapted from AASLD/IDA HCV Guidance, see hcvguidelines.org for most recent recommendations):

Table 1: AASLD/IDSA Guidance for initial treatment of patients initiating therapy for HCV infection (treatment naïve or previous relapsers) (adapted from AASLD/IDA HCV Guidance, see www.hcvguidelines.org for most recent recommendations)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Recommended Regimen</th>
</tr>
</thead>
</table>
| 1a       | 1. **Daklinza 60mg and Sovaldi 400mg for 12 weeks (no cirrhosis) or 24 weeks, with or without weight based ribavirin if cirrhosis present (Adjust Daklinza dose for drug interactions if needed), for treatment naïve patients with genotype 1a**  
2. Harvoni daily for 12 wk, for treatment naïve patients with genotype 1a **Harvoni for 8 weeks is an option if pretreatment HCV RNA level < 6million, but should be done with caution and at the discretion of the prescriber  
3. Viekira Pak with ribavirin for 12 wk (no cirrhosis) or 24 wk (with cirrhosis), for treatment naïve patients with genotype 1a  
4. Sovaldi + Olysio daily +/- ribavirin for 12 wk (no cirrhosis) or 24 wk (cirrhosis without the Q80k polymorphism), for treatment naïve patients with genotype 1a |
| 1b       | 1. **Daklinza 60mg and Sovaldi 400mg for 12 weeks (no cirrhosis) or 24 weeks, with or without weight based ribavirin (cirrhosis) (Adjust Daklinza dose for drug interactions if needed), for treatment naïve patients with genotype 1b**  
2. Harvoni daily for 12 weeks, for treatment naïve patients with genotype 1b  
3. Viekira Pak for 12 weeks, for treatment naïve patients with genotype 1b  
4. Sovaldi plus Olysio daily +/- ribavirin for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis), for treatment naïve patients with genotype 1b |
| 2        | 1. **Daklinza 60mg and Sovaldi 400mg for 12 weeks for patients who cannot tolerate ribavirin, for treatment naïve patients with genotype 2  
2. Sovaldi and ribavirin for 12 weeks (interferon-free regimen), for treatment naïve patients with genotype 2 [If cirrhosis, use of **Sovaldi and ribavirin with an extended duration of 16 weeks is recommended] |
| 3        | 1. Daklinza 60mg and Sovaldi 400mg for 12 weeks (no cirrhosis) or 24 weeks, with or without weight based ribavirin if patient has cirrhosis, for treatment naïve patients with genotype 3 (Adjust Daklinza dose for drug interactions if needed)  
2. **Sovaldi and peginterferon/ribavirin for 12 weeks for interferon eligible patients, for treatment naïve patients with genotype 3  
3. An alternative regimen is Sovaldi and ribavirin for 24 weeks for patients who are interferon ineligible, for treatment naïve patients with genotype 3 |
| 4        | 1. **Harvoni for 12 weeks, for treatment naïve patients with genotype 4  
2. Technivie and ribavirin for 12 weeks, for treatment naïve patients with genotype 4  
3. **Sovaldi and ribavirin for 24 weeks, for treatment naïve patients with genotype 4  
4. Alternative recommendation for genotype 4 is Sovaldi and peginterferon/ribavirin for 12 weeks |
| 5        | 1. **Harvoni for 12 weeks, for treatment naïve patients with genotype 5  
2. **Alternative treatment option is **Sovaldi + peginterferon/ribavirin for 12 weeks. |
| 6        | 1. **Harvoni for 12 weeks for treatment naïve patients with genotype 6  
2. **Alternative treatment option is **Sovaldi with peginterferon/ribavirin for 12 weeks |

** = Regimen is not FDA-approved for this genotype (off label use)
<table>
<thead>
<tr>
<th>GT</th>
<th>Previous agent/regimen failed</th>
<th>Recommended Regimen</th>
</tr>
</thead>
</table>
| 1a   | Peginterferon/ribavirin regimen                     | 1. Daklinza 60mg and Sovaldi 400mg for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis), with or without weight based ribavirin (cirrhosis), for treatment experienced, genotype 1a patients in whom peginterferon/ribavirin has failed (Adjust Daklinza dose for drug interactions if needed)  
2. Harvoni for 12 weeks (no cirrhosis)  
If cirrhosis: Harvoni and ribavirin for 12 weeks OR Harvoni for 24 weeks  
3. Viekira Pak for 12 weeks with ribavirin (no cirrhosis)  
If cirrhosis: Viekira Pak and ribavirin for 24 weeks  
4. Olysio plus Sovaldi for 12 weeks if no cirrhosis or 24 weeks if cirrhosis (for patients who do not have Q80K variant) |
| 1a   | Sovaldi regimen (with ribavirin, and with or without peginterferon) | 1. Harvoni with ribavirin for 12 weeks (no cirrhosis) or with ribavirin for 24 weeks (cirrhosis); If cirrhosis: Harvoni and RBV for 24 weeks                                                                                     |
| 1a   | 1. HCV protease inhibitor/peginterferon/ribavirin or 2) Olysio + Sovaldi | 1. Daklinza 60mg and Sovaldi 400mg for 12 weeks (no cirrhosis); or 24 weeks (cirrhosis), with or without weight based ribavirin for those with cirrhosis  
2. Harvoni for 12 weeks for patients without cirrhosis (Harvoni 12 week regimen is not recommended if patient has previously failed Olysio/Sovaldi regimen); Harvoni with ribavirin for 24 weeks if patient has cirrhosis |
| 1a or 1b | NS5A inhibitors                                      | Defer treatment if possible for patients with minimal liver disease. Test for resistance associated variants for NS3 protease inhibitors or NS5A inhibitors. Use 24 week duration regimens when possible, and add ribavirin if tolerated. |
| 1b   | Peginterferon/ribavirin regimen                      | 1. **Daklinza 60mg and Sovaldi 400mg for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis), with or without weight based ribavirin (cirrhosis), for treatment experienced, genotype 1a patients in whom peginterferon/ribavirin has failed (Adjust Daklinza dose for drug interactions if needed)  
2. Harvoni for 12 weeks (no cirrhosis)  
If cirrhosis: **Harvoni and ribavirin for 12 weeks or Harvoni for 24 weeks  
3. Viekira Pak for 12 weeks (for all patients, with or without cirrhosis; no ribavirin required for genotype 1b)  
4. Olysio + Sovaldi for 12 weeks if no cirrhosis or 24 weeks if cirrhosis |
| 1b   | Sovaldi regimen (with ribavirin, and with or without peginterferon) | 1. Harvoni with ribavirin for 12 weeks (no cirrhosis) or with ribavirin for 24 weeks (cirrhosis); If cirrhosis: **Harvoni and RBV for 24 weeks                                                                                      |
| 1b   | HCV protease                                        | 1. **Daklinza 60mg and Sovaldi 400mg for 12 weeks (no cirrhosis) or with ribavirin for 24 weeks (cirrhosis); If cirrhosis: **Harvoni and RBV for 24 weeks                                                                                  |
### Table 2: AASLD/IDSA Guidance for retreatment of HCV infection (recommendations for patients in whom previous peginterferon/ribavirin treatment has failed) (adapted from AASLD/IDA HCV Guidance, see www.hcvguidelines.org for most recent recommendations)

<table>
<thead>
<tr>
<th>GT</th>
<th>Previous agent/regimen failed</th>
<th>Recommended Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>inhibitor/ peginterferon/ribavirin or 5. 2) Olysio + Sovaldi</td>
<td>cirrhosis); or 24 weeks (cirrhosis), with or without weight based ribavirin for those with cirrhosis 2. Harvoni for 12 weeks for patients without cirrhosis (**add ribavirin for 12 weeks if patient has previously failed Olysio/Sovaldi regimen)</td>
</tr>
<tr>
<td>2</td>
<td>Peginterferon/ribavirin regimen</td>
<td>1. **Sovaldi with ribavirin for 16 or 24 weeks 2. **Alternative regimen is Sovaldi plus peginterferon/ribavirin for 12 weeks, for patients who are eligible to take interferon</td>
</tr>
<tr>
<td>2</td>
<td>Sovaldi regimen (with ribavirin)</td>
<td>3. **Daklinza 60mg and Sovaldi 400mg for 24 weeks (+/- ribavirin) for patients who cannot use interferon 4. **Sovaldi + peginterferon/ribavirin for 12 weeks</td>
</tr>
<tr>
<td>3</td>
<td>Peginterferon/ribavirin regimen</td>
<td>1. Daklinza 60mg and Sovaldi 400mg for 12 weeks (no cirrhosis); or 24 weeks (cirrhosis), with weight based ribavirin for those with cirrhosis. 2. **Sovaldi, peginterferon, and ribavirin for 12 weeks if patient is interferon eligible.</td>
</tr>
<tr>
<td>3</td>
<td>Sovaldi/ribavirin</td>
<td>1. Daklinza 60mg and Sovaldi 400mg for 24 weeks with weight based ribavirin, for interferon ineligible patients 2. Sovaldi, peginterferon, and ribavirin for 12 weeks if patient is interferon eligible.</td>
</tr>
<tr>
<td>4</td>
<td>Peginterferon/ribavirin regimen</td>
<td>1. **Harvoni for 12 weeks 2. Technivie with ribavirin for 12 weeks 3. **Sovaldi + peginterferon/ribavirin for 12 weeks if patient is interferon eligible 4. Sovaldi + ribavirin for 24 weeks</td>
</tr>
<tr>
<td>5</td>
<td>Peginterferon/ribavirin regimen</td>
<td>1. **Harvoni for 12 weeks 2. **Sovaldi, peginterferon, and ribavirin for 12 weeks if patient is interferon eligible.</td>
</tr>
<tr>
<td>6</td>
<td>Peginterferon/ribavirin regimen</td>
<td>1. **Harvoni for 12 weeks 2. **Sovaldi, peginterferon, and ribavirin for 12 weeks if patient is interferon eligible.</td>
</tr>
</tbody>
</table>

### Table 3: AASLD/IDSA Guidance for HCV infection in patients with decompensated cirrhosis (adapted from AASLD/IDA HCV Guidance, see www.hcvguidelines.org for most recent recommendations)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Recommended Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1. **Daklinza/Sovaldi with low-dose ribavirin (start at 600mg) for 12 weeks; use Daklinza/Sovaldi for 24 weeks for ribavirin-intolerant patients 2. **Harvoni with low-dose ribavirin for 12 weeks; use Harvoni and low-dose ribavirin for 24 weeks if patient has previously failed a Sovaldi regimen.</td>
</tr>
<tr>
<td>2</td>
<td>1. **Daklinza/Sovaldi and low dose ribavirin for 12 weeks 2. **Sovaldi and weight-based ribavirin for up to 48 weeks</td>
</tr>
</tbody>
</table>
Table 3: AASLD/IDSA Guidance for HCV infection in patients with decompensated cirrhosis
(adapted from AASLD/IDA HCV Guidance, see www.hcvguidelines.org for most recent recommendations)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Recommended Regimen</th>
</tr>
</thead>
</table>
| 3        | 1. **Daklinza/Sovaldi and low dose ribavirin for 12 weeks  
2. **Sovaldi and weight-based ribavirin for up to 48 weeks |

** = Regimen is currently not FDA-approved

Efficacy
The efficacy of Harvoni was evaluated in three phase III clinical trials (ION-1, ION-2, and ION-3); the studies enrolled a total of 1518 adults with genotype 1 chronic hepatitis C with compensated liver disease. The primary efficacy endpoint for all studies was SVR, defined as HCV RNA below the lower limit of quantification, at 12 weeks after the end of treatment (SVR12).

Table 1: Major phase III clinical trials for Harvoni

<table>
<thead>
<tr>
<th>Study</th>
<th>Clinical trial design</th>
<th>Patient population</th>
</tr>
</thead>
<tbody>
<tr>
<td>ION-1</td>
<td>randomized, open-label study</td>
<td>Treatment naïve patients, genotype 1, with or without cirrhosis (16% had cirrhosis)</td>
</tr>
<tr>
<td>ION-2</td>
<td>randomized, open-label study</td>
<td>Previously treated patients (previous failure with peginterferon/ribavirin or protease inhibitor triple therapy), genotype 1, with or without cirrhosis (20% had cirrhosis)</td>
</tr>
<tr>
<td>ION-3</td>
<td>randomized, open-label study</td>
<td>647 treatment naïve patients, genotype 1, without cirrhosis</td>
</tr>
</tbody>
</table>

CONTINUED ON NEXT PAGE
### EFFICACY (CONTINUED)

Efficacy outcomes for Harvoni (ledipasvir/sofosbuvir) with or without ribavirin (RBV) for treatment of genotype 1 infection: ION-1 and ION-2 clinical trials

<table>
<thead>
<tr>
<th></th>
<th>Harvoni - 12 weeks (GT 1)</th>
<th>Harvoni + RBV- 12 weeks (GT 1)</th>
<th>Harvoni – 24 weeks (GT 1)</th>
<th>Harvoni + RBV - 24 weeks (GT 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ION-1, Previously untreated patients (16% with cirrhosis)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary endpoint, SVR12 for all study patients</td>
<td>99% (210/213)*</td>
<td>97% (211/217)</td>
<td>98% (212/217)</td>
<td>99% (215/217)</td>
</tr>
<tr>
<td>SVR for patients with cirrhosis</td>
<td>94% (32/34)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>SVR for patients without cirrhosis</td>
<td>99% (176/177)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Virologic failure</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Relapse</td>
<td>&lt;1% (1/212)</td>
<td>0</td>
<td>&lt;1% (1/217)</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Harvoni - 12 weeks (GT 1)</th>
<th>Harvoni + RBV- 12 weeks (GT 1)</th>
<th>Harvoni – 24 weeks (GT 1)</th>
<th>Harvoni + RBV - 24 weeks (GT 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ION-2, Treatment-experienced patients (20% with cirrhosis)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary endpoint, SVR12</td>
<td>94%</td>
<td>96%</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>Virologic failure</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1% (1/111)</td>
</tr>
<tr>
<td>Relapse</td>
<td>6% (7/109)</td>
<td>4% (4/111)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* = SVR for various subgroups within ION-2 : patients with cirrhosis- SVR rate was 94% (32/34), patients with genotype 1a- SVR rate was 98% (142/145) and patients with genotype 1b – SVR rate was 100% (67/67)

CONTINUED ON NEXT PAGE
LEDIPASVIR/SOFOSBUVIR

EFFICACY (CONTINUED)
Efficacy outcomes for Harvoni (ledipasvir/sofosbuvir) for 8 or 12 weeks for treatment of genotype 1 infection in treatment naïve patients: ION-3 clinical trial

<table>
<thead>
<tr>
<th></th>
<th>Harvoni - 8 weeks (GT 1)</th>
<th>Harvoni – 12 weeks (GT 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint, SVR12</td>
<td>94% (202/215)*</td>
<td>95% (206/216)</td>
</tr>
<tr>
<td>for all study patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVR for those with baseline HCV RNA &lt; 6 million IU/mL</td>
<td>97% (119/123)</td>
<td>96% (126/131)</td>
</tr>
<tr>
<td>SVR by genotype, genotype 1a</td>
<td>93% (159/171)</td>
<td>96% (165/172)</td>
</tr>
<tr>
<td>SVR by genotype, genotype 1b</td>
<td>98% (42/43)</td>
<td>98% (43/44)</td>
</tr>
<tr>
<td>Relapse</td>
<td>5% (11/215)</td>
<td>1% (3/216)</td>
</tr>
<tr>
<td>Virologic failure</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

SAFETY
Adverse events reported in more than 10% of patients treated with Harvoni in clinical trials included fatigue and headache. Incidence varied by treatment duration (see below).

Table 4: Adverse reactions reported in greater than or equal to 5% of subjects receiving 8, 12 or 24 weeks of Harvoni (from Harvoni prescribing information):

<table>
<thead>
<tr>
<th></th>
<th>Harvoni 8 week regimen (n=215)</th>
<th>Harvoni 12 week regimen (n=539)</th>
<th>Harvoni 24 week regimen (n=326)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>16%</td>
<td>13%</td>
<td>18%</td>
</tr>
<tr>
<td>Headache</td>
<td>11%</td>
<td>14%</td>
<td>17%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6%</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4%</td>
<td>3%</td>
<td>7%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3%</td>
<td>5%</td>
<td>6%</td>
</tr>
</tbody>
</table>

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LEDIPASVIR/SOFOSBUVIR

SAFETY (CONTINUED)

Ledipasvir and sofosbuvir are both substrates of P-glycoprotein (P-gp), but are not metabolized by the CYPP450 pathway. Drug interactions with Harvoni include medications that are P-gp inducers such as rifampin and St John’s wort. Concurrent administration of Harvoni and P-gp inducers is not recommended. The following medications may decrease the concentrations of Harvoni: carbamazepine, phenytoin, phenobarbital, oxcarbazepine, rifampin, rifabutin, rifapentine, St. John’s Wort, or tipranavir/ritonavir; concurrent administration of these agents with Harvoni is not recommended. The following medications interact with Harvoni and an increase in their concentration may occur with coadministration with Harvoni: rosuvastatin and Stribild (elvitragravir/cobicistat/ emtricitabine/tenofovir); concurrent administration with Harvoni is not recommended. The concurrent use of simeprevir and Harvoni may increase serum concentrations of simeprevir; concurrent administration with Harvoni is not recommended. The use of Harvoni with other products containing sofosbuvir, such as Sovaldi, is not recommended. Concurrent use of Harvoni and amiodarone may increase the risk of symptomatic bradycardia and is not recommended.

The solubility of ledipasvir, a component of Harvoni, decreases as pH increases. Drugs that may increase gastric pH, such as antacids, H2 blockers, and proton pump inhibitors could decrease concentrations of ledipasvir. If the patient continues to use these medications while taking Harvoni, the manufacturer recommends the following:

- Patients using antacids while taking Harvoni should separate administration of the two medications by at least 4 hours.
- Patients using H2 blockers should use a dose equivalent to famotidine 40mg twice daily or less.
- Patients using proton pump inhibitors should use a dose equivalent to omeprazole 20mg daily or less.

Patients using digoxin while taking Harvoni may experience an increase in digoxin levels. Therapeutic concentration monitoring of digoxin levels while on Harvoni is recommended.

The safety and efficacy of Harvoni has not been established in pediatric patients. No dosage adjustment is required for geriatric patients, or for those with mild to moderate renal impairment. The safety and efficacy of Harvoni has not been established in patients with severe renal impairment (eGFR less than 30mL/minute/1.73m²) or end stage renal disease requiring hemodialysis.

No dosage requirement is necessary for patients with mild, moderate or severe hepatic impairment (Child Pugh Class A, B or C). The safety and efficacy of Harvoni has not been established in patients with decompensated cirrhosis.

Harvoni is Pregnancy category B. Harvoni has not been adequately studied in pregnant humans, but animal studies of Harvoni during pregnancy show no effects on fetal development.

CONTINUED ON NEXT PAGE
REFERENCES