Ledipasvir-Sofosbuvir (*Harvoni*)

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**Drug Summary**

The fixed-dose combination of ledipasvir-sofosbuvir provides an effective and well-tolerated one-pill once-a-day option for treatment of genotypes 1, 4, 5, and 6 chronic hepatitis C (HCV) infection. This direct-acting antiviral regimen was the first FDA-approved interferon- and ribavirin free regimen to treat hepatitis C. Ledipasvir-sofosbuvir can be used without ribavirin in most patients with genotype 1A, except those who are cirrhotic and treatment-experienced. In addition, patients who are treatment-naïve, not black, and without cirrhosis may be eligible for an 8-week duration which has been found in clinical trials and observational studies to be as effective as 12 weeks. Like sofosbuvir-velpatasvir, the other NS5B-NS5A inhibitor combination, it has been shown to be safe and efficacious in patients with decompensated cirrhosis.

**Adverse Effects**

Available data from clinical trials has demonstrated the combination of ledipasvir-sofosbuvir has been very well tolerated. The most common reported adverse effects are fatigue and headache.

**Class and Mechanism**
Ledipasvir is a potent inhibitor of HCV NS5A, a viral phosphoprotein that plays an important role in viral replication, assembly, and secretion. Sofosbuvir is a nucleotide analog inhibitor of hepatitis C virus NS5B polymerase—the key enzyme mediating HCV RNA replication. The triphosphate form of sofosbuvir (GS-461203) mimics the natural cellular uridine nucleotide and is incorporated by the HCV RNA polymerase into the elongating RNA primer strand, resulting in viral chain termination.

Manufacturer for United States

Harvoni (har-VOE-nee) is a fixed-dose combination of ledipasvir and sofosbuvir (Figure 1) and (Figure 2). It is manufactured by Gilead Sciences.

FDA Status

On October 10, 2014, the fixed-dose combination ledipasvir-sofosbuvir (Harvoni) was approved by the FDA for the treatment of chronic hepatitis C genotype 1 infection in adults. On November 12, 2015 the FDA expanded the approval of ledipasvir-sofosbuvir to include (a) treatment of chronic hepatitis C genotypes 4, 5, and 6 and (b) patients coinfected with HIV. On February 12, 2016 the FDA further expanded the approval of ledipasvir-sofosbuvir to include (a) treatment of chronic hepatitis C genotypes 1 and 4 in liver transplant recipients without cirrhosis or compensated cirrhosis, and (b) patients with genotype 1 infection who have decompensated cirrhosis.

Indications

The fixed dose combination ledipasvir-sofosbuvir (90 mg/400 mg) is indicated for treatment, with or without ribavirin, for the treatment of patients with chronic hepatitis C genotypes 1, 4, 5, and 6. The detailed indications are listed below. When treating patients coinfected with HCV and HIV, the recommendations are the same as listed below.

**Genotype 1**

- Treatment-naïve without cirrhosis or with compensated cirrhosis (Child-Pugh A) : ledipasvir-sofosbuvir x 12 weeks*
- Treatment-experienced** without cirrhosis: ledipasvir-sofosbuvir x 12 weeks
- Treatment-experienced** with compensated cirrhosis (Child-Pugh A): ledipasvir-sofosbuvir x 24 weeks†
- Treatment naïve and treatment experienced** with decompensated cirrhosis (Child-Pugh B or C): ledipasvir-sofosbuvir plus ribavirin‡ x 12 weeks

**Genotype 1 or 4**

- Treatment-naïve and treatment-experienced ** liver transplant recipients without cirrhosis, or with compensated cirrhosis (Child-Pugh A): ledipasvir-sofosbuvir plus ribavirin‡ x 12 weeks

**Genotype 4, 5, or 6**
• Treatment-naïve and treatment-experienced ** without cirrhosis or with compensated cirrhosis (Child-Pugh A): ledipasvir-sofosbuvir plus ribavirin x 12 weeks

Footnotes
*Based on a sub-analysis from the ION-3 trial, ledipasvir-sofosbuvir for 8 weeks can be considered in treatment-naïve genotype 1 patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL.

**Treatment-experienced patients include those who have failed a peginterferon alfa plus ribavirin based regimen, with or without an HCV protease inhibitor.

†Ledipasvir-sofosbuvir for 12 weeks can be considered in treatment-experienced genotype 1 patients with cirrhosis who are eligible for ribavirin (see footnote§ for ribavirin dosage recommendations).

‡In patients with decompensated cirrhosis, the starting dosage of ribavirin is 600 mg and can be titrated up to 1000 mg for patients Figure 2). The recommended dosage is one tablet once daily, with or without food.

• For patients with mild to moderate renal impairment, no dosage adjustment of ledipasvir-sofosbuvir is recommended. There are insufficient data regarding the safety and efficacy of ledipasvir-sofosbuvir in patients with severe renal impairment (eGFR less than 30 ml/min/1.73m²) or end-stage renal disease requiring dialysis. Thus, no dosage recommendation has been given for patients with severe renal impairment or end-stage renal disease requiring dialysis.
• For patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C), no dosage adjustment is recommended, but the safety and efficacy of ledipasvir-sofosbuvir in patients with decompensated cirrhosis has not been established.

Clinical Use

The combination of ledipasvir-sofosbuvir has primarily been studied as an all-oral (interferon-free) combination regimen in treatment-naïve and treatment-experienced patients with genotype 1 chronic HCV infection. Phase 3 studies (ION-1, ION-2, and ION-3) have consistently shown SVR12 rates greater than 90% with a 12-week course of ledipasvir-sofosbuvir in patients with genotype 1 chronic HCV. For treatment-experienced patients with cirrhosis, the SVR12 rates were significantly better with 24 weeks of therapy than with 12 weeks. A subanalysis of the ION-3 trial showed that treatment-naïve patients without cirrhosis had excellent SVR12 rates with only 8 weeks of ledipasvir-sofosbuvir if their pre-treatment HCV RNA level was less than 6 million IU/mL. For the treatment-naïve patients with genotype 1 infection, the addition of ribavirin to ledipasvir-sofosbuvir did not provide significant benefit. Ledipasvir-sofosbuvir is a preferred regimen for initial treatment and retreatment of patients with genotypes 1, 4, 5, or 6 chronic hepatitis C infection. In addition, ledipasvir-sofosbuvir is indicated for the treatment of hepatitis C in persons coinfected with HIV.

Cost and Medication Access

The wholesale acquisition cost (WAC) for ledipasvir-sofosbuvir is $1125 per pill.

• Cost of 8-week course of therapy = $63,000
• Cost of 12-week course of therapy = $94,500
• Cost of 24-week course of therapy = $189,000
Gilead Sciences has an active ledipasvir-sofosbuvir patient assistance program for eligible patients with hepatitis C who do not have insurance and do not have coverage through Medicaid or Medicare. Information regarding the Gilead Sciences ledipasvir-sofosbuvir (Harvoni) patient assistance program can be obtained at the Support Path for Solvaldi and Harvoni web site and by contacting them directly by phone at 1-855-769-7284 (hours of operation Monday through Friday between 9:00 am and 8:00 pm Eastern Time).

### Resistance

In vitro, ledipasvir can select for the primary NS5A mutations Q30E and Y93H with genotype 1a and Y93H with genotype 1b; these mutations confer high-level reduced susceptibility to ledipasvir. In phase 3 trials, the most common mutations detected at failure for genotype 1a were Q30R, Y93H or N, and L31M; with genotype 1b, the most common mutation was Y93H. In vitro, the substitution S282T is associated with a 2- to 18-fold reduced susceptibility to sofosbuvir. The S282T mutation was not detected in any of the ledipasvir-sofosbuvir phase 3 trials. Ledipasvir has excellent in vitro activity against the NS5B S282T mutants. Similarly, sofosbuvir retains full activity against the NS5A ledipasvir-associated mutations.

### Key Drug Interactions

For complete information on ledipasvir-sofosbuvir-related drug interactions, see the Drug Interactions section in the Ledipasvir-Sofosbuvir (Harvoni) Prescribing Information.

### Full Prescribing Information

Ledipasvir-sofosbuvir (Harvoni) Full Prescribing Information.