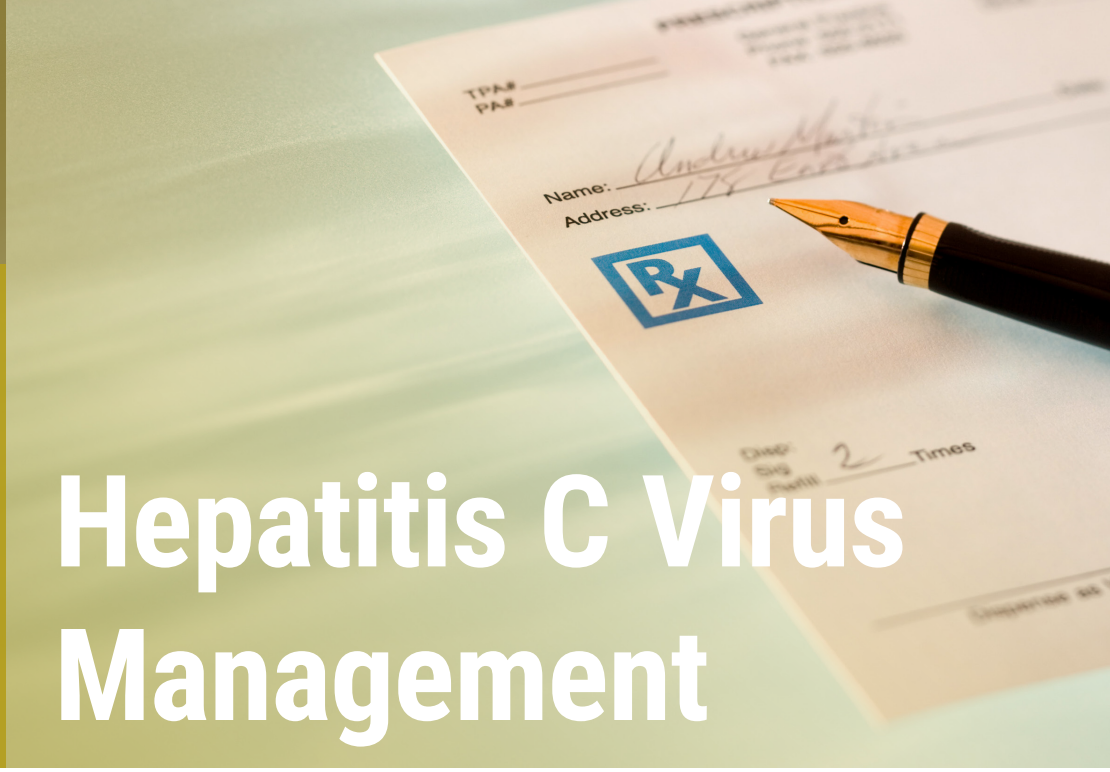

Hepatitis C Virus Management

Hepatitis C is caused by a virus and results in liver inflammation, which can lead to advanced liver disease and/or liver cancer. An estimated 3 to 4 million individuals in the U.S. are infected with the hepatitis C virus (HCV). There are six genotypes of the HCV, of which genotype 1 is the most common cause of infections in the U.S. and genotype 4 is the least common.[1]

The Pharmacy & Therapeutics Committee has approved a multi-level approach to managing chronic hepatitis C virus (HCV) medications. These medications include Daklinza®, Epclusa®, Harvoni ®, Olysio®, Sovaldi®, Technivie®, Viekira Pak®, Viekira XR®, and Zepatier®.

FDA-Approved Medications

Currently, there are at least two direct-acting antiviral medications approved by the U.S. Food and Drug Administration (FDA) for each of the six genotypes.[2-10] Table 1 compares the FDA-approved indications for the direct-acting antiviral medications. Prescribing information is updated regularly for these medications; always consult package labeling for current information.

Clinical Treatment Guidelines

Treatment guidelines for testing, managing, and treating hepatitis C have been developed by the American Association for the Study of Liver Disease (AASLD) and the Infectious Diseases Society of America (IDSA), in collaboration with the International Antiviral Society USA (IAS-USA). These guidelines are updated regularly to include new developments and were last updated on July 6, 2016.[11]

Current recommendations for the treatment and retreatment of genotype 1 infected patients are summarized in Table 2 and Appendix A, respectively.[12,13] The current update does not include the new formulation of Viekira, Viekira XR, but it is anticipated to be included for use in the same patient populations as Viekira Pak.

The guidelines also include the recommended regimens for the following treatment-naïve patients: genotype 2, 3, and 4 without cirrhosis and with compensated cirrhosis, and for genotype 5/6 with and without cirrhosis. Alternatives to the recommended regimen — as well as regimens not recommended — are also provided in the guidelines for treatment-naïve patients.[12] Treatment recommendations also exist for unique patient populations, including: HIV/HCV co-infection, decompensated cirrhosis, recurrent HCV infection post-liver transplant, and renal impairment.[14] Visit hcvguidelines.org for current recommendations.

Formulary Management

The agents summarized in Table 1 and 2 are on the standard NPS formularies. This inclusive approach acknowledges the clinical differences of the medications and aligns with AASLD and IDSA treatment guidelines. For plans with a specialty tier, all HCV products are offered on the specialty tier. For plans without a specialty tier, the P&T Committee designated Daklinza, Epclusa, Harvoni, Olysio, Sovaldi, and Zepatier as non-preferred, and Technivie, Viekira Pak, and Viekira XR as preferred.

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Table 1: Comparison of FDA-Approved Indications for Direct-Acting Antiviral Medications

Brand (generic)	Genotypes	In combination with another DAA	Ribavirin (RBV) Required	Liver Function	Duration of Therapy	Special Populations	AWP for 12 Week Treatment Course
Daklinza (daclatasvir)	1[o] or 3	With sofosbuvir	With or without (dependent on genotype and liver status)	Without cirrhosis Compensated cirrhosis Decompensated cirrhosis	12 weeks	Post-transplant HCV/HIV-1 co-infection	$75,600
Epclusa (sofosbuvir/ velpatasvir)	1, 2, 3, 4, 5, 6	N/A	With RBV for decompensated cirrhosis	Without cirrhosis Compensated cirrhosis	12 weeks	N/A	$89,712
Harvoni (ledipasvir/ sofosbuvir)	1, 4, 5, or 6	N/A	With* or without	Without cirrhosis Compensated cirrhosis Decompensated cirrhosis**	8, 12, or 24 weeks+	Liver-transplant recipients‡ HCV/HIV-1 co-infection	$113,400
Olysio (simeprevir)	1∞ or 4	With sofosbuvir (genotype 1)	With PEG-IFN/RBV (genotype 1 or 4)	Without cirrhosis Compensated cirrhosis	12 or 24 weeks	HCV/HIV-1 co-infection (in combination with PEG-IFN/ RBV)	$79,632
Sovaldi (sofosbuvir)	1, 2, 3, or 4	with PEG-IFN/ ribavirin (genotype 1 or 4)	With RBV (genotype 2 or 3)	Not specified in package labeling	12 or 24 weeks	HCV/HIV-1 co-infection; hepatocellular carcinoma awaiting liver transplant	$100,800
Technivie (ombitasvir/ paritaprevir/ ritonavir)	4	N/A	With RBV§	Without cirrhosis	12 weeks	N/A	$91,983.60
Viekira Pak Viekira XR (ombitasvir/ paritaprevir/ ritonavir/ dasabuvir)	1a and 1b	N/A	RBV is required for patients with genotype 1a.	Without cirrhosis Compensated cirrhosis	12 or 24 weeks	HCV/HIV co-infection; liver transplant recipients with normal hepatic function and mild fibrosisα	$99,982.80
Zepatier (elbasvir/ grazoprevir)	1β or 4	N/A	With γ or without RBV	Without cirrhosis Compensated cirrhosis	12 or 16 weeksγ	HCV/HIV-1 co-infection	$65,520

Definitions and Abbreviations: Compensated cirrhosis = Child Pugh A; decompensated cirrhosis = Child Pugh B or C; PEG-IFN = PEG-interferon alfa; RBV = ribavirin

[o] Daklinza: For patients with genotype 1a with cirrhosis, testing for the presence of NS5A resistance-associated polymorphisms should be considered before initiation.

***** Harvoni: For the following indications, it is used in combination with ribavirin: genotype 1 treatment-naïve and treatment-experienced patients with decompensated cirrhosis; genotype 1 or 4 treatment-naïve and treatment-experienced liver transplant recipients without cirrhosis or with compensated cirrhosis.

****** Harvoni: Indicated for genotype 1 treatment-naive and treatment-experienced patients with decompensated cirrhosis.

+ Harvoni: For treatment-naïve genotype 1 patients without cirrhosis who have pretreatment HCV RNA less than 6 million IU/mL, 8 weeks of Harvoni may be considered. The duration of treatment is usually 12 or 24 weeks and is dependent on genotype, liver status, and treatment history.

‡ Harvoni: indicated for genotype 1 or 4 treatment-naïve and treatment-experienced liver transplant recipients without cirrhosis or with compensated cirrhosis.

∞ Olysio: For patients with genotype 1a who are to receive Olysio in combination with PEG-interferon alfa and ribavirin, testing for the presence of virus with NS3 Q80K polymorphism is strongly recommended before initiation of therapy. If Q80K is detected, alternative therapy should be considered

§ Technivie: Without ribavirin may be considered for treatment-navie patients who cannot take or tolerate ribavirin.

α Viekira: Mild fibrosis = Metavir fibrosis score 2 or lower

β Zepatier: For genotype 1a, recommended to test for presence of virus with NS5A resistance-associated polymorphisms before initiation.

γ Zepatier: Whether it is used in combination with ribavirin and the duration of treatment are dependent on the virus genotype/subtype (1a, 1b, or 4), presence or absence of NS5A polymorphisms (for genotype 1a patients), and past treatment history.

Table 2: Initial Recommended Regimens for Treatment of HCV Genotype 1 Infection According to the AASLD-IDSA Guidance[12]

Patient Population	Regimen	Available Products	Duration	Level of Evidence
Genotype 1a or Genotype 1b, treatment-naïve, without cirrhosis	Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)*	Zepatier®	12 weeks	Class I, Level A
	Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	Harvoni®	12 weeks	Class I, Level A
	Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dasabuvir (250 mg) with weight-based ribavirin+	Viekira Pak® + ribavirin+	12 weeks	Class I, Level A
	Daily simeprevir (150 mg) plus sofosbuvir (400 mg)	Olysio® + Sovaldi®	12 weeks	Class I, Level A
	Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	Epclusa®	12 weeks	Class I, Level A
	Daily daclatasvir (60 mg‡) plus sofosbuvir (400 mg)	Daklinza® + Sovaldi®	12 weeks	Class I, Level B
Genotype 1a, treatment-naïve, compensated cirrhosis	Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)*	Zepatier®	12 weeks	Class I, Level A
	Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	Harvoni®	12 weeks	Class I, Level A
	Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	Epclusa®	12 weeks	Class I, Level A
Genotype 1b, treatment-naïve, compensated cirrhosis	Daily fixed-dose combination of grazoprevir (100 mg)/elbasvir (50 mg)	Zepatier®	12 weeks	Class I, Level A
	Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	Harvoni®	12 weeks	Class I, Level A
	Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg)§	Viekira Pak®	12 weeks	Class I, Level A
	Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	Epclusa®	12 weeks	Class I, Level A

***** This recommendation applies to Genotype 1a patients in whom no baseline high fold-change NS5A resistance-associated variants for elbasvir are detected. This includes genotype 1a polymorphisms at amino acid positions 28, 30, 31, or 93.

+ Weight-based ribavirin is only a recommended component of the regimen for Genotype 1a patients, not for Genotype 1b patients.

‡ The dose of daclatasvir may need to be increased or decreased when used in combination with cytochrome P450 3A/4 inducers and inhibitors.

§ The FDA has issued a warning regarding the use of Viekira Pak in patients with underlying advanced liver disease. As a result, use is contraindicated in patients with moderate and severe hepatic impairment (Child-Pugh B and C).[7,8,9,12]

Utilization Management

All HCV medications require prior authorization on the standard NPS formularies to encourage appropriate utilization according to their FDA-approved indications and recently updated treatment guidelines issued by AASLD/IDSA/IAS-USA. Prior authorization of all agents supports Viekira as the preferred agent for HCV genotype 1 and Technivie as the preferred agent for HCV genotype 4. Consideration for coverage of the other products for genotype 1 or 4 will be given for patients who have contraindications to treatment with these agents. In addition to the prior authorization requirement, the HCV medications will each have a quantity limit to encourage appropriate utilization and reduce waste.

Cost Analysis

Table 3 provides a cost analysis for genotype 1 treatments, as recommended by the current guidelines. The treatment costs of Viekira Pak and Technivie are less than listed below due to rebates. Viekira XR is not included in Table 3 as it is not addressed in the most recent guideline update, but Viekira XR is anticipated to be used in the same patient populations as Viekira Pak. Although Viekira Pak is dosed as four tablets per day and Viekira XR is dosed as three extended-release tablets per day, the AWP per tablet is priced such that the cost per day of either formulation — Viekira Pak or Viekira XR — is the same.

Table 3: Cost of Initial Recommended Regimens for Treatment of HCV Genotype 1 Infection[12]

Patient Population	Commercially Available Product(s)	Dosing Regimen	Duration	Cost of Treatment (AWP)*
Genotype 1a or Genotype 1b, treatment-naïve, without cirrhosis	Zepatier®	1 tablet once daily	12 weeks	$65,520
	Harvoni®	1 tablet once daily	12 weeks	$113,400
	Viekira Pak® + ribavirin	2 tablets of ombitasvir/paritaprevir/ritonavir once daily; 1 tablet of dasabuvir twice daily +/- ribavirin twice daily	12 weeks	$100,638 Viekira Pak: $99,982.80 ribavirin: $655.20‡
	Olysio® + Sovaldi®	1 capsule of Olysio once daily; 1 tablet of Sovaldi once daily	12 weeks	$180,432 Olysio:$79,632 Sovaldi: $100,800
	Epclusa®	1 tablet once daily	12 weeks	$89,712
	Daklinza® + Sovaldi®	1 tablet of Daklinza once daily; 1 tablet of Sovaldi once daily	12 weeks	$176,400 Daklinza: $75,600 Sovaldi: $100,800
Genotype 1a, treatment-naïve, compensated cirrhosis	Zepatier®	1 tablet once daily	12 weeks	$65,520
	Harvoni®	1 tablet once daily	12 weeks	$113,400
	Epclusa®	1 tablet once daily	12 weeks	$89,712
Genotype 1b, treatment-naïve, compensated cirrhosis	Zepatier®	1 tablet once daily	12 weeks	$65,520
	Harvoni®	1 tablet once daily	12 weeks	$113,400
	Viekira Pak®	2 tablets of ombitasvir/paritaprevir/ ritonavir once daily; 1 tablet of dasabuvir twice daily	12 weeks	$99,982.80
	Epclusa®	1 tablet once daily	12 weeks	$89,712

***** Ribavirin cost is based on MAC price of a 200 mg ribavirin capsule ($1.30 per capsule).

‡ Dosing based on body weight of 75 kg (1200 mg per day, 6 capsules per day).

References

1. Hepatitis C FAQs for Health Professionals. Centers for Disease Control and Prevention Website. Available at : http://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#d1. Updated January 8, 2016. Accessed February 1, 2016.
2. Daklinza (daclatasvir) package insert. Bristol-Myers Squibb Company. Princeton, NJ. April 2016. Available at : http://packageinserts.bms.com/pi/pi_daklinza.pdf.
3. Epclusa (sofosbuvir/velpatasvir) package insert. Gilead Sciences, Inc. Foster City, CA. June 2016. Available at : http://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/epclusa/epclusa_pi.pdf.
4. Harvoni (ledipasvir/sofosbuvir) package insert. Gilead Sciences, Inc. Foster City, CA. June 2016. Available at : http://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/harvoni/harvoni_pi.pdf.
5. Olysio (simeprevir) package insert. Janssen Products, LP. Titusville, NJ. May 2016. Available at: https://www.olysio.com/shared/product/olysio/prescribing-information.pdf.
6. Sovaldi (sofosubvir) package insert. Gilead Sciences, Inc. Foster City, CA. August 2015. Available at : http://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/sovaldi/sovaldi_pi.pdf.
7. Technivie (ombitasvir, paritaprevir, and ritonavir) package insert. AbbVie Inc. North Chicago, IL. June 2016. Available at : http://www.rxabbvie.com/pdf/technivie_pi.pdf.
8. Viekira Pak (ombitasvir, paritaprevir, and ritonavir tablets ; dasabuvir tablets) package insert. AbbVie Inc. North Chicago, IL. January 2016. Available at : http://www.rxabbvie.com/pdf/viekirapak_pi.pdf.
9. Viekira XR (dasabuvir, ombitasvair, paritaprevir, ritonavir ER tablets) package insert. AbbVie Inc. North Chicago, IL. July 2016. Available at : http://www.rxabbvie.com/pdf/viekiraxr_pi.pdf.
10. Zepatier (elbasvir and grazoprevir) tablets. Merck & Co., Inc. Whitehouse Station, NJ. January 2016. Available at : http://www.merck.com/product/usa/pi_circulars/z/zepatier/zepatier_pi.pdf.
11. AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. Available at : http://www.hcvguidelines.org. Updated February 24, 2016. Accessed March 18, 2016.
12. AASLD-IDSA. Initial Treatment Box. Summary of Recommendations for Patients Who are Initiating Therapy for HCV Infection by HCV Genotype. Available at : http://hcvguidelines.org/node/72. Updated July 6, 2016. Accessed March 18, 2016. ASSLD-IDSA. Retreatment Box. Summary of Recommendations for Patients in Whom Prevoius Treatment Has Failed. Updated July 6, 2016. Available at : http://hcvguidelines.org/node/74. Updated February 24, 2016. Accessed March 18, 2016.
13. AASLD-IDSA. HCV Guidance : Recommendations for Testing, Managing, and Treating Hepatitis C. http://www.hcvguidelines.org/full-report-view. Updated February 24, 2016. Accessed March 18, 2016.

Appendix A, Table 4: Recommended Regimens for Retreatment of HCV Genotype 1 Infection in Persons Whom Failed Prior Therapy[13]

Patient Population	Regimen	Available Products	Duration	Level of Evidence
Genotype 1a or Genotype 1b PEG-interferon/ribavirin treatment-experienced, without cirrhosis	Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)*	Zepatier®	12 weeks	Class I, Level A
	Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	Harvoni®	12 weeks	Class I, Level A
	Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ ombitasvir (25 mg) plus twice-daily dasabuvir (250 mg) and weight-based ribavirin+	Viekira Pak® + ribavirin+	12 weeks	Class I, Level A
	Daily simeprevir (150 mg) plus sofosbuvir (400 mg)	Olysio® + Sovaldi®	12 weeks	Class I, Level A
	Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	Epclusa®	12 weeks	Class I, Level A
	Daily daclatasvir (60 mg‡) plus sofosbuvir (400 mg)	Daklinza® + Sovaldi®	12 weeks	Class I∞, Level B
Genotype 1a, PEG-interferon/ribavirin treatment-experienced, compensated cirrhosis	Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)*	Zepatier®	12 weeks	Class I, Level A
	Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	Epclusa®	12 weeks	Class I, Level A
	Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin	Harvoni® + ribavirin	12 weeks	Class I, Level A
Genotype 1b, PEG-interferon/ribavirin treatment-experienced, compensated cirrhosis	Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	Zepatier®	12 weeks	Class I, Level A
	Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin	Harvoni® + ribavirin	12 weeks	Class I, Level A
	Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	Epclusa®	12 weeks	Class I, Level A
	Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) §	Viekira Pak®	12 weeks	Class I, Level A

*****This recommendation applies to Genotype 1a patients in whom no baseline high fold-change NS5A resistance-associated variants for elbasvir are detected. This includes genotype 1a polymorphisms at amino acid positions 28, 30, 31, or 93 (amino acid substitutions that result in resistance).

+Weight-based ribavirin is only a recommended component of regimen for Genotype 1a patients, not for Genotype 1b patients.

‡The dose of daclatasvir may need to be increased or decreased when used in combination with cytochrome P450 3A/4 inducers and inhibitors.

∞For Genotype 1b, the recommendation is Class IIa, Level B.

§The FDA has issued a warning regarding the use of Viekira Pak in patients with underlying advanced liver disease. As a result, use is contraindicated in patients with moderate and severe hepatic impairment (Child-Pugh B and C).[7,8,9,12]

Appendix B, Table 5: Cost of Recommended Retreatment Regimens for HCV Genotype 1 Infection in Persons Whom Failed Prior Therapy[13]

Patient Population	Commercially Available Products	Dosing Regimen	Duration	Cost of Treatment (AWP)*
Genotype 1a or Genotype 1b PEG-interferon/ ribavirin treatment-experienced, without cirrhosis	Zepatier®	1 tablet once daily	12 weeks	$65,520
	Harvoni®	1 tablet once daily	12 weeks	$113,400
	Viekira Pak® + ribavirin	2 tablets of ombitasvir/paritaprevir/ ritonavir once daily; 1 tablet of dasabuvir twice daily +/- ribavirin twice daily	12 weeks	$100,638 Viekira Pak: $99,982.80 ribavirin: $655.20‡
	Olysio® + Sovaldi®	1 capsule of Olysio® once daily; 1 tablet of Sovaldi® once daily	12 weeks	$180,432 Olysio: $79,632 Sovaldi: $100,800
	Epclusa®	1 tablet once daily	12 weeks	$89,712
	Daklinza® + Sovaldi®	1 tablet of Daklinza once daily; 1 tablet of Sovaldi once daily	12 weeks	$176,400 Daklinza: $75,600 Sovaldi: $100,800
Genotype 1a, PEG-interferon/ ribavirin treatment-experienced, compensated cirrhosis	Zepatier®	1 tablet once daily	12 weeks	$65,520
	Epclusa®	1 tablet once daily	12 weeks	$89,712
	Harvoni® + ribavirin	1 Harvoni® tablet once daily; ribavirin twice daily	12 weeks	$114,055.20 Harvoni: $113,400 ribavirin: $655.20‡
Genotype 1b, PEG-interferon/ ribavirin treatment-experienced, with compensated cirrhosis	Zepatier®	1 tablet once daily	12 weeks	$65,520
	Harvoni® + ribavirin	1 Harvoni® tablet once daily; ribavirin twice daily	12 weeks	$114,055.20 Harvoni: $113,400 ribavirin: $655.20‡
	Epclusa®	1 tablet once daily	12 weeks	$89,712
	Viekira Pak®	2 tablets of ombitasvir/paritaprevir/ritonavir once daily; 1 tablet of dasabuvir twice daily	12 weeks	$99,982.80

* Ribavirin cost is based on MAC price of a 200 mg ribavirin capsule ($1.30 per capsule).

‡ Dosing based on body weight of 75 kg (1200 mg per day, 6 capsules per day).

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