Hepatitis C Therapy includes the following products:

- **Oral Direct-Acting Antiviral Agents**
  - Daclatasvir (Daklinza™)
  - Elbasvir/grazoprevir (Zepatier™)
  - Glecaprevir/pibrentasvir (Mavyret™)
  - Ledipasvir/sofosbuvir (Harvoni®)
  - Ombitasvir/paritaprevir/ritonavir (Technivie™)
  - Ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak™/Viekira XR™)
  - Simeprevir (Olysio®)
  - Sofosbuvir (Sovaldi®)
  - Sofosbuvir/velpatasvir (Epclusa®)
  - Sofosbuvir/velpatasvir/voxilaprevir (Vosevi™)

* Preferred therapies for Employer Group Benefit Plans include: Epclusa, Harvoni, Mavyret, Sovaldi, and Vosevi
** Preferred therapies for Individual and Family Benefit Plans include: Epclusa, Harvoni, and Sovaldi

- **Interferon Therapy**
  - interferon alfa-2b (Intron® A)
  - peginterferon alfa-2a (Pegasys®)
  - peginterferon alfa-2b (PegIntron®)

For all non-hepatitis C criteria for interferon and pegylated interferon therapy, please refer to coverage policy #1315, Interferon Therapy, using the link above.
The standards for effective management of hepatitis C, including recommendations regarding treatment initiation and the medication regimens utilized for treatment are evolving rapidly as data from clinical trials and guidelines from national organizations become available. Further changes are likely as additional alternatives are approved by the FDA. Therefore, coverage criteria are subject to change to remain up-to-date. Please check for updates regularly to be sure you have the latest criteria.

Cigna covers Hepatitis C Therapy as medically necessary for the treatment of chronic hepatitis C virus (HCV) infection when ALL of the following criteria AND the specified criteria for the requested regimen are met:

- Baseline quantitative HCV-RNA testing (e.g., within 3 months of planned therapy initiation)
- HCV genotype (and subtype when applicable)
- Documentation of the degree of hepatic fibrosis (i.e., Metavir score or alternative – refer to Appendix 1) by liver biopsy or noninvasive testing (unless clinically evident cirrhosis)
- For individuals with decompensated cirrhosis, recurrence of HCV infection post-liver transplantation, kidney transplant recipients, or with severe renal impairment (including end stage renal disease): Prescriber of therapy should be a gastroenterologist, infectious disease specialist, or transplant specialist
- Commitment to participate in a hepatitis C disease state management program

Regimen Specific Criteria for Oral Direct-Acting Antiviral Agents

- **Daklinza (daclatasvir) and Sovaldi (sofosbuvir) Combination Therapy**
  - Treatment of an adult and ONE of the following is met:
    - **Genotype 1 HCV infection** and BOTH of the following:
      - No prior treatment with NS5A inhibitors or NS5B inhibitors
      - ONE of the following:
        - **Absence of cirrhosis or presence of compensated cirrhosis** and BOTH of the following:
          - ONE of the following:
            - For Employer Group Benefit Plans: Not a candidate for ledipasvir/sofosbuvir (Harvoni), sofosbuvir/velpatasvir (Epclusa), AND glecaprevir/pibrentasvir (Mavyret)
            - For Individual & Family Benefit Plans: Not a candidate for ledipasvir/sofosbuvir (Harvoni)
        - **Presence of decompensated cirrhosis** (moderate or severe hepatic impairment; Child-Turcotte-Pugh class B or C [see Appendix 2]) AND not a candidate for ledipasvir/sofosbuvir (Harvoni) and for Employer Group Benefit Plans only: not a candidate for sofosbuvir/velpatasvir (Epclusa) – Treatment duration authorization = 12 weeks in combination with ribavirin; 24 weeks if ribavirin ineligible
      - **Recurrence of HCV infection post-liver transplantation** AND not a candidate for ledipasvir/sofosbuvir (Harvoni) – Treatment duration authorization = 12 weeks in combination with ribavirin; 24 weeks if ribavirin ineligible
    - **Genotype 2 HCV infection** and BOTH of the following:
      - No prior treatment with HCV protease inhibitors, NS5A inhibitor, or NS5B inhibitors
      - ONE of the following:
        - **Absence of cirrhosis or presence of compensated cirrhosis** and BOTH of the following:
          - ONE of the following:
            - For Employer Group Benefit Plans: Not a candidate for sofosbuvir/velpatasvir (Epclusa) AND glecaprevir/pibrentasvir (Mavyret)
            - For Individual & Family Benefit Plans: Not a candidate for sofosbuvir/velpatasvir (Epclusa)
        - Treatment naïve to HCV therapy - Treatment duration authorization = 12 weeks (up to 24 weeks if presence of compensated cirrhosis)
        - Treatment-experienced with pegylated interferon and ribavirin - Treatment duration authorization = 12 weeks (up to 24 weeks if presence of compensated cirrhosis)
• **Presence of decompensated cirrhosis** (moderate or severe hepatic impairment; Child-Turcotte-Pugh class B or C [see Appendix 2]) – Treatment duration authorization = 12 weeks in combination with ribavirin; 24 weeks if ribavirin ineligible
• **Recurrence of HCV infection post-liver transplantation** – Treatment duration authorization = 12 weeks in combination with ribavirin; 24 weeks if ribavirin ineligible

• **Genotype 3 HCV infection** and BOTH of the following:
  o No prior treatment with HCV protease inhibitors or NS5A inhibitors
  o ONE of the following:
    • **Absence of cirrhosis or presence of compensated cirrhosis** and BOTH of the following:
      • ONE of the following:
        o For Employer Group Benefit Plans: Not a candidate for sofosbuvir/velpatasvir (Epclusa) AND glecaprevir/pibrentasvir (Mavyret)
        o For Individual & Family Benefit Plans: Not a candidate for sofosbuvir/velpatasvir (Epclusa)
      • ONE of the following:
        o Treatment naïve to HCV therapy - Treatment duration authorization = 12 weeks (in combination with ribavirin for compensated cirrhosis)
        o Treatment-experienced with pegylated interferon and ribavirin - Treatment duration authorization = 12 weeks (in combination with ribavirin for compensated cirrhosis)
  o **Presence of decompensated cirrhosis** (moderate or severe hepatic impairment; Child-Turcotte-Pugh class B or C [see Appendix 2]) AND not a candidate for sofosbuvir/velpatasvir (Epclusa) – Treatment duration authorization = 12 weeks in combination with ribavirin; 24 weeks if ribavirin ineligible
  o **Recurrence of HCV infection post-liver transplantation** – Treatment duration authorization = 12 weeks in combination with ribavirin; 24 weeks if ribavirin ineligible

➤ **Epclusa (sofosbuvir/velpatasvir)**
  Treatment of an adult and ONE of the following is met:
  • **Genotype 1 or 4 HCV infection** and ONE of the following:
    o Absence of cirrhosis and BOTH of the following:
      • No prior treatment with NS5A inhibitors
      • ONE of the following:
        • Treatment-naïve to HCV therapy OR treatment-experienced with pegylated interferon and ribavirin with or without an HCV protease inhibitor – Treatment duration authorization = 12 weeks
        • **Genotype 1b HCV infection**: Treatment-experienced with sofosbuvir-containing regimen – Treatment duration authorization = 12 weeks
    o Presence of compensated cirrhosis and BOTH of the following:
      • No prior treatment with NS5A inhibitors
      • ONE of the following:
        • Treatment-naïve – Treatment duration authorization = 12 weeks
        • Treatment-experienced with pegylated interferon and ribavirin with or without an HCV protease inhibitor – Treatment duration authorization = 12 weeks
        • **Genotype 1b HCV infection**: Treatment-experienced with sofosbuvir-containing regimen – Treatment duration authorization = 12 weeks
    o Presence of decompensated cirrhosis (moderate or severe hepatic impairment; Child-Turcotte-Pugh class B or C [see Appendix 2]) and ONE of the following:
      • **Genotype 1 HCV infection** – Treatment duration authorization = 12 weeks in combination with ribavirin or 24 weeks if ribavirin ineligible (24 weeks in combination with ribavirin for prior failure with a sofosbuvir-containing or NS5A-containing regimen)
      • **Genotype 4 HCV infection** - Treatment duration authorization = 12 weeks in combination with ribavirin or 24 weeks if ribavirin ineligible (24 weeks in combination with ribavirin for prior failure with a sofosbuvir-containing regimen)
  • **Genotype 2 or 3 HCV infection** and ONE of the following:
    o Absence of cirrhosis or presence of compensated cirrhosis and BOTH of the following:
- No prior treatment with NS5A inhibitors
- ONE of the following:
  - Treatment-naïve to HCV therapy – *Treatment duration authorization = 12 weeks*
  - Treatment-experienced with pegylated interferon and ribavirin – *Treatment duration authorization = 12 weeks*
  - For Genotype 2 HCV infection: Treatment-experienced with sofosbuvir and ribavirin – *Treatment duration authorization = 12 weeks*
- **Presence of decompensated cirrhosis** (moderate or severe hepatic impairment; Child-Turcotte-Pugh class B or C [see Appendix 2]) – *Treatment duration authorization = 12 weeks in combination with ribavirin or 24 weeks if ribavirin ineligible (24 weeks in combination with ribavirin for prior failure with a sofosbuvir-containing or NS5A-containing regimen)*
- **Recurrence of HCV infection post-liver transplantation** (with compensated or decompensated cirrhosis) – *Treatment duration authorization = 12 weeks in combination with ribavirin*
- **Genotype 5 or 6 HCV infection** and ONE of the following:
  - Absence of cirrhosis or presence of compensated cirrhosis and BOTH of the following:
    - No prior treatment with NS5A inhibitors or NS5B inhibitors
    - Treatment-naïve to HCV therapy OR treatment-experienced with pegylated interferon and ribavirin - *Treatment duration authorization = 12 weeks*
  - **Presence of decompensated cirrhosis** (moderate or severe hepatic impairment; Child-Turcotte-Pugh class B or C [see Appendix 2]) – *Treatment duration authorization = 12 weeks in combination with ribavirin or 24 weeks if ribavirin ineligible (24 weeks in combination with ribavirin for prior failure with a sofosbuvir-containing regimen)*
- **Harvoni (ledipasvir/sofosbuvir)** – EITHER of the following:
  1. Treatment of an adult and BOTH of the following are met:
     - No prior treatment with NS5A inhibitors
     - ONE of the following is met:
       - Genotype 1 HCV infection and ONE of the following:
         - Absence of cirrhosis and ONE of the following:
           - Treatment-naïve to HCV therapy – *Treatment duration authorization = 12 weeks (8 weeks for non-black, HIV-uninfected, and HCV RNA level less than 6 million IU/mL)*
           - Treatment-experienced with pegylated interferon and ribavirin with or without an HCV protease inhibitor - *Treatment duration authorization = 12 weeks*
           - Treatment-experienced with a sofosbuvir/ribavirin with or without pegylated interferon regimen – *Treatment duration authorization = 12 weeks in combination with ribavirin*
       - Presence of compensated cirrhosis and ONE of the following:
         - Treatment-naïve to HCV therapy - *Treatment duration authorization = 12 weeks*
         - Treatment-experienced with pegylated interferon and ribavirin with or without an HCV protease inhibitor - *Treatment duration authorization = 12 weeks in combination with ribavirin or 24 weeks if ribavirin ineligible*
         - Presence of decompensated cirrhosis (moderate or severe hepatic impairment; Child-Turcotte-Pugh class B or C [see Appendix 2]) – *Treatment duration authorization = 12 weeks in combination with ribavirin or 24 weeks if ribavirin ineligible (24 weeks in combination with ribavirin for prior failure with a sofosbuvir-containing regimen)*
         - Recurrence of HCV infection post-liver transplantation (including compensated and decompensated cirrhosis) – *Treatment duration authorization = 12 weeks in combination with ribavirin*
         - Kidney transplant recipient (absence of cirrhosis or presence of compensated cirrhosis)– *Treatment duration authorization = 12 weeks*
  2. Genotype 4 HCV infection and ONE of the following:
     - Absence of cirrhosis or presence of compensated cirrhosis AND treatment naïve to HCV therapy or treatment-experienced with pegylated interferon and ribavirin – *Treatment duration authorization = 12 weeks*
     - Presence of decompensated cirrhosis (moderate or severe hepatic impairment; Child-Turcotte-Pugh class B or C [see Appendix 2]) – *Treatment duration authorization = 12 weeks in combination with ribavirin or 24 weeks if ribavirin ineligible*
with ribavirin or 24 weeks if ribavirin ineligible (24 weeks in combination with ribavirin for prior failure with a sofosbuvir-containing regimen)

- **Recurrence of HCV infection post-liver transplantation** (including compensated and decompensated cirrhosis) – *Treatment duration authorization = 12 weeks in combination with ribavirin*
- **Kidney transplant recipient** (absence of cirrhosis or presence of compensated cirrhosis) – *Treatment duration authorization = 12 weeks*

  - **Genotype 5 or 6 HCV infection** and ONE of the following:
    - **Absence of cirrhosis or presence of compensated cirrhosis** and treatment-naïve to HCV therapy or treatment-experienced with pegylated interferon and ribavirin with or without an HCV protease inhibitor – *Treatment duration authorization = 12 weeks*
    - **Presence of decompensated cirrhosis** (moderate or severe hepatic impairment; Child-Turcotte-Pugh class B or C [see Appendix 2]) – *Treatment duration authorization = 12 weeks in combination with ribavirin or 24 weeks if ribavirin ineligible (24 weeks in combination with ribavirin for prior failure with a sofosbuvir-containing regimen)*
    - **Recurrence of HCV infection post-liver transplantation** (including compensated and decompensated cirrhosis) – *Treatment duration authorization = 12 weeks in combination with ribavirin*

2) **Treatment of a pediatric individual 12 years of age and older OR weighing at least 35 kg** and **BOTH** of the following:

- Treatment naïve to HCV therapy OR treatment-experienced with interferon/pegylated interferon with or without ribavirin
- **ONE** of the following:
  - **Genotype 1 HCV infection** and ONE of the following:
    - **Absence of cirrhosis** – *Treatment duration authorization = 12 weeks*
    - **Presence of compensated cirrhosis** – *Treatment duration authorization = 12 weeks for treatment naïve and 24 weeks for treatment-experienced*
  - **Genotype 4, 5, or 6 HCV infection** AND absence or presence of compensated cirrhosis – *Treatment duration authorization = 12 weeks*

  ➢ **Mavyret (glecaprevir/pibrentasvir)**

  **Treatment of an adult and ALL of the following:**

  - No prior treatment an NS5A inhibitor and an HCV NS3/4A protease inhibitor (either in combination or as components of separate treatment regimens)
  - Absence of moderate or severe hepatic impairment (Child-Turcotte-Pugh B or C [see Appendix 2])
  - **ONE** of the following is met:
    - **Genotype 1 HCV infection** and ONE of the following:
      - **Absence of cirrhosis or presence of compensated cirrhosis** and ONE of the following:
        - Treatment-naïve to HCV therapy or treatment-experienced with pegylated interferon/ribavirin AND for Individual & Family Plans ONLY: not a candidate for ledipasvir/sofosbuvir (Harvoni) (for example, severe renal impairment [eGFR less than 30 mL/min]) – *Treatment duration authorization = 8 weeks for non-cirrhotics and 12 weeks for compensated cirrhosis*
        - Treatment-experienced with an NS3/4A protease inhibitor with pegylated interferon/ribavirin AND for Individual & Family Plans ONLY: not a candidate for ledipasvir/sofosbuvir (Harvoni) (for example, severe renal impairment [eGFR less than 30 mL/min]) – *Treatment duration authorization = 12 weeks*
        - Treatment-experienced with sofosbuvir, ribavirin with or without pegylated interferon - *Treatment duration authorization = up to 12 weeks*
        - Treatment-experienced with sofosbuvir in combination with simeprevir - *Treatment duration authorization = 12 weeks*
        - Treatment-experienced with an NS5A inhibitor - *Treatment duration authorization = 16 weeks*
      - **Recurrence of HCV infection post-liver transplantation** – *Treatment duration authorization = 12 weeks*
      - **Kidney transplant recipient** – *Treatment duration authorization = 12 weeks*
Genotype 2 HCV infection and ONE of the following:

- Absence of cirrhosis or presence of compensated cirrhosis and ONE of the following:
  - Treatment-naïve to HCV therapy or treatment-experienced with pegylated interferon/ribavirin AND for Individual & Family Plans ONLY: not a candidate for sofosbuvir/velpatasvir (Epclusa) (for example, severe renal impairment [eGFR less than 30 mL/min]) - Treatment duration authorization = 8 weeks for non-cirrhotics and 12 weeks for compensated cirrhosis
  - Treatment-experienced with sofosbuvir, ribavirin with or without pegylated interferon - Treatment duration authorization = up to 12 weeks
- Recurrence of HCV infection post-liver transplantation – Treatment duration authorization = 12 weeks
- Kidney transplant recipient – Treatment duration authorization = 12 weeks

Genotype 3 HCV infection and ONE of the following:

- Absence of cirrhosis or presence of compensated cirrhosis and ONE of the following:
  - Treatment-naïve to HCV therapy AND for Individual & Family Plans ONLY: Not a candidate for sofosbuvir/velpatasvir (Epclusa) (for example, severe renal impairment [eGFR less than 30 mL/min]) – Treatment duration authorization = 8 weeks for non-cirrhotics and 12 weeks for compensated cirrhosis
  - Treatment-experienced with pegylated interferon/ribavirin AND for Individual & Family Plans ONLY: Not a candidate for sofosbuvir/velpatasvir (Epclusa) (for example, severe renal impairment [eGFR less than 30 mL/min]) – Treatment duration authorization = 16 weeks
  - Treatment-experienced with sofosbuvir, ribavirin with or without pegylated interferon – Treatment duration authorization = 16 weeks
- Recurrence of HCV infection post-liver transplantation – Treatment duration authorization = 12 weeks
- Kidney transplant recipient – Treatment duration authorization = 12 weeks

Genotype 4 HCV infection and ONE of the following:

- Absence of cirrhosis or presence of compensated cirrhosis and ONE of the following:
  - Treatment-naïve to HCV therapy or treatment-experienced with pegylated interferon/ribavirin – AND for Individual & Family Plans ONLY: not a candidate for ledipasvir/sofosbuvir (Harvoni) (for example, severe renal impairment [eGFR less than 30 mL/min]) – Treatment duration authorization = 8 weeks for non-cirrhotics and 12 weeks for compensated cirrhosis
  - Treatment-experienced with sofosbuvir, ribavirin with or without pegylated interferon - Treatment duration authorization = 8 weeks for non-cirrhotics and 12 weeks for compensated cirrhosis
- Recurrence of HCV infection post-liver transplantation – Treatment duration authorization = 12 weeks
- Kidney transplant recipient – Treatment duration authorization = 12 weeks

Genotype 5 or 6 HCV infection and ONE of the following:

- Absence of cirrhosis or presence of compensated cirrhosis and ONE of the following:
  - Treatment-naïve to HCV therapy or treatment-experienced with pegylated interferon/ribavirin – AND for Individual & Family Plans ONLY: Not a candidate for ledipasvir/sofosbuvir (Harvoni) (for example, severe renal impairment [eGFR less than 30 mL/min]) – Treatment duration authorization = 8 weeks for non-cirrhotics and 12 weeks for compensated cirrhosis
  - Treatment-experienced with sofosbuvir, ribavirin with or without pegylated interferon - Treatment duration authorization = 8 weeks for non-cirrhotics and 12 weeks for compensated cirrhosis
- Recurrence of HCV infection post-liver transplantation – Treatment duration authorization = 12 weeks
- Kidney transplant recipient – Treatment duration authorization = 12 weeks

Olysio (simeprevir) and Sovaldi (sofosbuvir) Combination Therapy

Treatment of an adult and ALL of the following are met:
- ONE of the following:
加工政策编号：1316

对雇主福利团体计划

- 不符合 ledipasvir/sofosbuvir (Harvoni),
- sofosbuvir/velpatasvir (Epclusa), AND glecaprevir/pibrentasvir (Mavyret)

对个人及家庭福利计划

- 不符合 ledipasvir/sofosbuvir (Harvoni)

- 无前次治疗HCV的蛋白酶抑制剂，NS5A抑制剂，或NS5B抑制剂
- 补偿性肝病
- ONE其中一项：
  - Genotype 1a or 1b HCV感染，无肝硬化
    - 治疗授权期限 = 12周
  - Genotype 1a HCV感染，有肝硬化
    - 无NS3 Q80K变异
    - 治疗授权期限 = 24周
  - Genotype 1b HCV感染，有肝硬化
    - 治疗授权期限 = 24周

- Sovaldi (sofosbuvir)
  
  BOTH的条件均满足：
  - 无前次治疗NS5A抑制剂或NS5B抑制剂
  - ONE其中一项：
    - 治疗成人
    - 治疗对象
      - 肝细胞癌等待肝移植的成人
        - 具有1, 2, 3, 或4 HCV感染
        - 治疗授权期限 = 不超过48周
        - 肝细胞癌
        - 治疗授权期限 = 12周
      - Genotype 3 HCV感染
        - 与Zepatier (elbasvir/grazoprevir)结合使用
        - 治疗授权期限 = 12周
    - Genotype 3 HCV感染
      - 治疗授权期限 = 24周

- Technivie (ombitasvir/paritaprevir/ritonavir)
  
  全部条件均满足：
  - 无前次治疗HCV的蛋白酶抑制剂，NS5A抑制剂，或NS5B抑制剂
  - Genotype 4 HCV感染
  - 无中度或严重肝损伤（Child-Pugh B或Child-Pugh C）
  - ONE其中一项：
    - 治疗成人
    - 治疗授权期限 = 12周
    - 治疗成人
    - 治疗授权期限 = 12周

- Viekira Pak/Viekira XR (ombitasvir/paritaprevir/ritonavir and dasabuvir)
  
  治疗条件全部满足：
  - 无前次治疗HCV的蛋白酶抑制剂，NS5A抑制剂，或NS5B抑制剂
  - 无中度或严重肝损伤（Child-Pugh B或Child-Pugh C）
  - ONE其中一项：
    - Genotype 1a HCV感染
      - 肝细胞癌
      - 与Zepatier (elbasvir/grazoprevir)结合使用
      - 治疗授权期限 = 12周
    - Genotype 3 HCV感染
      - 治疗授权期限 = 24周

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健康政策编号：1316
• For Employer Benefit Group Plans: Not a candidate for ledipasvir/sofosbuvir (Harvoni), sofosbuvir/velpatasvir (Epclusa), AND glecaprevir/pibrentasvir (Mavyret)
• For Individual & Family Benefit Plans: Not a candidate for ledipasvir/sofosbuvir (Harvoni)
  ▪ ONE of the following:
  ▪ Absence of cirrhosis – Treatment duration authorization = 12 weeks in combination with ribavirin
  ▪ Presence of compensated cirrhosis – Treatment duration authorization = up to 24 weeks in combination with ribavirin
  o Genotype 1b HCV infection and BOTH of the following:
    ▪ ONE of the following:
      ▪ For Employer Benefit Group Plans: Not a candidate for ledipasvir/sofosbuvir (Harvoni), sofosbuvir/velpatasvir (Epclusa), AND glecaprevir/pibrentasvir (Mavyret)
      ▪ For Individual & Family Benefit Plans: Not a candidate for ledipasvir/sofosbuvir (Harvoni)
    ▪ Absence of cirrhosis or presence of compensated cirrhosis – Treatment duration authorization = 12 weeks
  o Post-liver transplant, genotype 1 HCV infection with Metavir F0-F2 AND not a candidate for ledipasvir/sofosbuvir (Harvoni) – Treatment duration authorization = 24 weeks in combination with ribavirin

➤ Vosevi (sofosbuvir/velpatasvir/voxilaprevir)
Treatment of an adult and BOTH of the following are met:
• Absence of moderate or severe hepatic impairment (Child-Turcotte-Pugh B or C)
• ONE of the following:
  o Genotype 1 HCV infection and ONE of the following:
    ▪ Treatment-experienced with an NS5A inhibitor
    ▪ Genotype 1a and treatment-experienced with a sofosbuvir-containing regimen
  o Genotype 2 HCV infection and treatment-experienced with an NS5A inhibitor
  o Genotype 3 HCV infection and ONE of the following:
    ▪ Treatment-naïve with compensated cirrhosis AND presence of Y93H substitution
    ▪ Treatment-experienced with pegylated interferon/ribavirin without cirrhosis AND presence of Y93H substitution
    ▪ Treatment-experienced with pegylated interferon/ribavirin with compensated cirrhosis
    ▪ Treatment-experienced with an NS5A inhibitor
    ▪ Treatment-experienced with sofosbuvir without an NS5A inhibitor
  o Genotype 4, 5, or 6 HCV infection and treatment-experienced with an NS5A inhibitor OR treatment-experienced with sofosbuvir

Treatment duration authorization = 12 weeks

➤ Zepatier (elbasvir/grazoprevir)
Treatment of an adult and ALL of the following are met:
• No prior treatment with NS5A inhibitors or NS5B inhibitors
• Absence of moderate or severe hepatic impairment (Child-Pugh B or C)
• ONE of the following:
  o Genotype 1a HCV infection and BOTH of the following:
    ▪ ONE of the following:
      ▪ For Employer Benefit Group Plans: Not a candidate for ledipasvir/sofosbuvir (Harvoni) and sofosbuvir/velpatasvir (Epclusa) (for example, severe renal impairment [eGFR less than 30 mL/min]) AND not a candidate for glecaprevir/pibrentasvir (Mavyret)
      ▪ For Individual & Family Benefit Plans: Not a candidate for ledipasvir/sofosbuvir (Harvoni) (for example, severe renal impairment [eGFR less than 30 mL/min])
    ▪ ONE of the following:
      ▪ Treatment naïve to HCV therapy OR treatment experienced with pegylated interferon/ribavirin AND documentation of NS5A polymorphism testing
        o No baseline NS5A polymorphisms – Treatment duration authorization = 12 weeks
        o Presence of baseline NS5A polymorphisms at amino acid positions 28, 30, 31, or 93 – Treatment duration authorization = 16 weeks in combination with ribavirin

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• Treatment-experienced with an HCV protease inhibitor with pegylated interferon/ribavirin – 
  Treatment duration authorization = 12 weeks in combination with ribavirin (up to 16 weeks may 
  be considered for presence of NS5A polymorphisms at amino acid positions 28, 30, 31, or 93).
  
  o **Genotype 1b HCV infection** and BOTH of the following:
    
    - ONE of the following:
      
      - **For Employer Benefit Group Plans:** Not a candidate for ledipasvir/sofosbuvir (Harvoni) and 
        sofosbuvir/velpatasvir (Epclusa) (for example, severe renal impairment [eGFR less than 30 
        mL/min]) AND not a candidate for glecaprevir/pibrentasvir (Mavyret)
      
      - **For Individual & Family Benefit Plans:** Not a candidate for ledipasvir/sofosbuvir (Harvoni) (for 
        example, severe renal impairment [eGFR less than 30 mL/min])

  o Genotype 3 HCV infection and BOTH of the following:
    
    - Will be used in combination with Sovaldi (sofosbuvir)
    
    - Treatment-experienced with pegylated interferon and ribavirin with compensated cirrhosis – 
      Treatment duration authorization = 12 weeks

  o Genotype 4 HCV infection and BOTH of the following:
    
    - ONE of the following:
      
      - **For Employer Benefit Group Plans:** Not a candidate for ledipasvir/sofosbuvir (Harvoni) and 
        sofosbuvir/velpatasvir (Epclusa) (for example, severe renal impairment [eGFR less than 30 
        mL/min]) AND not a candidate for glecaprevir/pibrentasvir (Mavyret)
      
      - **For Individual & Family Benefit Plans:** Not a candidate for ledipasvir/sofosbuvir (Harvoni) (for 
        example, severe renal impairment [eGFR less than 30 mL/min])

    - ONE of the following:
      
      - Treatment naïve to HCV therapy – Treatment duration authorization = 12 weeks
      
      - Treatment-experienced with pegylated interferon/ribavirin – Treatment duration authorization = 
        16 weeks in combination with ribavirin

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### Regimen Specific Criteria for Interferon Therapy

**Pegasys**

- HCV infection in a pediatric individual (age 5-17 years old) with or without ribavirin AND previously 
  untreated with interferon alfa (Treatment duration authorization = 48 weeks)

**PegIntron**

- HCV infection in a pediatric individual (age 3-17 years old) with ribavirin (Treatment duration authorization = 
  48 weeks)

**Intron A**

- HCV infection in a pediatric individual (age 3-17 years old) in combination with ribavirin AND previously 
  untreated with interferon alfa (Treatment duration authorization for genotype 1 = 48 weeks; genotype 2 and 
  3 = 24 weeks)

Cigna does not cover the use of simeprevir (Olysio) when combined with pegylated interferon and 
ribavirin for genotype 1 HCV infection because it is considered not medically necessary due to the 
superiority of other available regimens (e.g., ledipasvir/sofosbuvir [Harvoni]).

Cigna does not cover the use of sofosbuvir (Sovaldi) when combined with pegylated interferon and 
ribavirin for HCV infection because it is considered not medically necessary as it is no longer a 
recommended regimen by the American Association for the Study of Liver Diseases (AASLD) and 
Infectious Diseases Society of America (IDSA).

Cigna does not cover the use of Hepatitis C Therapy for any other indication because it is considered 
experimental, investigational or unproven.
When coverage is available and medically necessary, the dosage, frequency, site of administration, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to Hepatitis C Therapy.

## FDA Approved Indications

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Approved Indication</th>
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<tbody>
<tr>
<td><strong>Oral Direct-Acting Antivirals</strong></td>
<td></td>
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| Daklinza (daclatasvir) | Daklinza is indicated for use with sofosbuvir, with or without ribavirin, for the treatment of patients with chronic hepatitis C virus (HCV) genotype 1 or genotype 3 infection [see Dosage and Administration (2) and Clinical Studies (14)]. limitations of Use:  
  * Sustained virologic response (SVR12) rates are reduced in HCV genotype 3-infected patients with cirrhosis receiving Daklinza in combination with sofosbuvir for 12 weeks [see Clinical Studies (14.2)]. |  
| Epclusa (sofosbuvir/ velpatasvir) | Epclusa is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5 or 6 infection [see Dosage and Administration (2.1) and Clinical Studies (14)]:  
  * without cirrhosis or with compensated cirrhosis  
  * with decompensated cirrhosis for use in combination with ribavirin |  
| Harvoni (ledipasvir/ sofosbuvir) | Harvoni is indicated with or without ribavirin for the treatment of adult patients with chronic hepatitis C virus (HCV) [see Dosage and Administration (2.2) and Clinical Studies (14)]:  
  * genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis  
  * genotype 1 infection with decompensated cirrhosis, for use in combination with ribavirin  
  * genotype 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis, for use in combination with ribavirin.  
  **Pediatric Patients:**  
  Harvoni is indicated for the treatment of pediatric patients 12 years of age and older or weighing at least 35 kg with HCV genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis [see Dosage and Administration (2.3) and Clinical Studies (14.6)]. |  
| Mavyret (glecaprevir/ pibrentasvir) | Mavyret is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A). Mavyret is also indicated for the treatment of adult patients with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor (PI), but not both [see Dosage and Administration (2.2) and Clinical Studies (14)]. |  
| Olysio (simeprevir) | Olysio is indicated for the treatment of adults with chronic hepatitis C virus (HCV) infection [see Dosage and Administration (2.2) and Clinical Studies(14)]:  
  * in combination with sofosbuvir in patients with HCV genotype 1 without cirrhosis or with compensated cirrhosis  
  * in combination with peginterferon alfa (Peg-IFN-alfa) and ribavirin (RBV) in patients with HCV genotype 1 or 4 without cirrhosis or with compensated cirrhosis.  
  **Limitations of Use:**  
  * Efficacy of Olysio in combination with Peg-IFN-alfa and RBV is substantially reduced in patients infected with HCV genotype 1a with an NS3 Q80K polymorphism at baseline compared to patients infected with hepatitis C virus (HCV) genotype 1a without the Q80K polymorphism [see Dosage and Administration (2.1) and Microbiology (12.4)]. |
<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Approved Indication</th>
</tr>
</thead>
</table>
| **Sovaldi** (sofosbuvir)    | Adult Patients: Sovaldi is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) infection as a component of a combination antiviral treatment regimen [see Dosage and Administration (2.2), and Clinical Studies (14)]  
|                             | • genotype 1 or 4 infection without cirrhosis or with compensated cirrhosis for use in combination with pegylated interferon and ribavirin  
|                             | • genotype 2 or 3 infection without cirrhosis or with compensated cirrhosis for use in combination with ribavirin.  
|                             | Pediatric Patients: Sovaldi is indicated for the treatment of chronic HCV genotype 2 or 3 infection in pediatric patients 12 years of age and older or weighing at least 35 kg without cirrhosis or with compensated cirrhosis for use in combination with ribavirin [see Dosage and Administration (2.3) and Clinical Studies (14.5)]. |
| **Technivie** (ombitasvir/paritaprevir/ritonavir) | Technivie is indicated in combination with ribavirin for the treatment of patients with genotype 4 chronic hepatitis C virus (HCV) infection without cirrhosis or with compensated cirrhosis [see Clinical Studies (14)]. |
| **Viekira Pak/Viekira XR** (ombitasvir/paritaprevir/ritonavir and dasabuvir) | Viekira Pak/Viekira XR is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) [see Dosage and Administration and Clinical Studies]:  
|                             | • genotype 1b without cirrhosis or with compensated cirrhosis  
|                             | • genotype 1a without cirrhosis or with compensated cirrhosis for use in combination with ribavirin. |
| **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir) | Vosevi is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have [see Dosage and Administration (2.2) and Clinical Studies (14)]:  
|                             | • genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor.  
|                             | • genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.  
|                             | o Additional benefit of Vosevi over sofosbuvir/velpatasvir was not shown in adults with genotype 1b, 2, 4, 5, or 6 infection previously treated with sofosbuvir without an NS5A inhibitor. |
| **Zepatier** (elbasvir/grazoprevir) | Zepatier is indicated for the treatment of chronic hepatitis C virus (HCV) genotype 1 or 4 infection in adults.  
|                             | Zepatier is indicated for use with ribavirin in certain patient populations [see Dosage and Administration (2.2)]. |
| **Interferon Therapy**      |                                                                                      |
| **Intron A** (interferon alfa-2b) | Chronic Hepatitis C  
|                             | Intron A is indicated for the treatment of chronic hepatitis C in patients 18 years of age or older with compensated liver disease who have a history of blood or blood-product exposure and/or are HCV antibody positive. Studies in these patients demonstrated that Intron A therapy can produce clinically meaningful effects on this disease, manifested by normalization of serum alanine aminotransferase (ALT) and reduction in liver necrosis and degeneration.  
|                             | A liver biopsy should be performed to establish the diagnosis of chronic hepatitis. Patients should be tested for the presence of antibody to HCV. Patients with other causes of chronic hepatitis, including autoimmune hepatitis, should be excluded. Prior to initiation of Intron A therapy, the physician should establish that the patient has compensated liver disease. The following patient |
entrance criteria for compensated liver disease were used in the clinical studies and should be considered before Intron A treatment of patients with chronic hepatitis C:

- No history of hepatic encephalopathy, variceal bleeding, ascites, or other clinical signs of decompensation
- Bilirubin - Less than or equal to 2 mg/dL
- Albumin - Stable and within normal limits
- Prothrombin Time - Less than 3 seconds prolonged
- WBC - Greater than or equal to 3000/mm3
- Platelets - Greater than or equal to 70,000/mm3

Serum creatinine should be normal or near normal.

Prior to initiation of Intron A therapy, CBC and platelet counts should be evaluated in order to establish baselines for monitoring potential toxicity. These tests should be repeated at Weeks 1 and 2 following initiation of Intron A therapy, and monthly thereafter. Serum ALT should be evaluated at approximately 3-month intervals to assess response to treatment (see Dosage and Administration).

Patients with preexisting thyroid abnormalities may be treated if thyroid-stimulating hormone (TSH) levels can be maintained in the normal range by medication. TSH levels must be within normal limits upon initiation of Intron A treatment and TSH testing should be repeated at 3 and 6 months (see Precautions, Laboratory Tests).

Intron A in combination with Rebetol® is indicated for the treatment of chronic hepatitis C in patients 3 years of age and older with compensated liver disease previously untreated with alpha interferon therapy and in patients 18 years of age and older who have relapsed following alpha interferon therapy. See Rebetol prescribing information for additional information.

Intron A is also indicated for hairy cell leukemia, malignant melanoma, follicular lymphoma, condylomata acuminata, AIDS-related Kaposi’s sarcoma, and chronic hepatitis B.

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Approved Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegasys (peginterferon alfa-2a)</td>
<td>Chronic Hepatitis C (CHC)</td>
</tr>
<tr>
<td>PegIntron (peginterferon alfa-2b)</td>
<td>Chronic Hepatitis B (CHB)</td>
</tr>
</tbody>
</table>

Pegasys, as part of a combination regimen with other hepatitis C virus (HCV) antiviral drugs, is indicated for the treatment of adults with chronic hepatitis C (CHC) with compensated liver disease. For information about the safe and effective use of other HCV antiviral drugs to be used in combination with Pegasys, refer to their prescribing information. Pegasys in combination with ribavirin is indicated for treatment of pediatric patients 5 years of age and older with CHC and compensated liver disease. Pegasys monotherapy is only indicated for the treatment of patients with CHC with compensated liver disease if there are contraindications or significant intolerance to other HCV antiviral drugs.

Limitations of Use:
- Pegasys alone or in combination with ribavirin without additional HCV antiviral drugs is not recommended for treatment of patients with CHC who previously failed therapy with an interferon-alfa.
- Pegasys is not recommended for treatment of patients with CHC who have had solid organ transplantation.

Pegasys is indicated for the treatment of adult patients with HBeAg-positive and HBeAg-negative chronic hepatitis B infection who have compensated liver disease and evidence of viral replication and liver inflammation.

PegIntron, as part of a combination regimen, is indicated for the treatment of Chronic Hepatitis C (CHC) in patients with compensated liver disease:
- PegIntron in combination with Rebetol® (ribavirin) and an approved Hepatitis C Virus (HCV) NS3/4A protease inhibitor is indicated in adult patients with HCV genotype 1 infection (see labeling of the specific HCV NS3/4A protease inhibitor for further information).
Brand Name | Approved Indication
--- | ---
 | • PegIntron in combination with Rebetol is indicated in patients with genotypes other than 1, pediatric patients (3-17 years of age), or in patients with genotype 1 infection where use of an HCV NS3/4A protease inhibitor is not warranted based on tolerability, contraindications or other clinical factors.

PegIntron monotherapy should only be used in the treatment of CHC in patients with compensated liver disease if there are contraindications to or significant intolerance of Rebetol and is indicated for use only in previously untreated adult patients. Combination therapy provides substantially better response rates than monotherapy [see Clinical Studies (14.1, 14.2)].

**FDA Recommended Dosing**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>FDA Recommended Dosing</th>
</tr>
</thead>
</table>
| Daklinza (daclatasvir) | **Testing Prior to Initiation of Therapy**  
*Testing for HBV infection:* Test all patients for evidence of current or prior HBV infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) before initiating HCV treatment with Daklinza [see Warnings and Precautions (5.1)].  

*NS5A Resistance Testing in HCV Genotype 1a-Infected Patients with Cirrhosis:* Consider screening for the presence of NS5A polymorphisms at amino acid positions M28, Q30, L31, and Y93 in patients with cirrhosis who are infected with HCV genotype 1a prior to the initiation of treatment with Daklinza and sofosbuvir with or without ribavirin [see Microbiology (12.4), Table 11].  

**Recommended Dosage**  
The recommended dosage of Daklinza is 60 mg, taken orally, once daily with or without food [see Clinical Pharmacology (12.3)].  

Table 1 provides the recommended Daklinza-containing treatment regimens and duration based on HCV genotype and patient population. The optimal duration of Daklinza and sofosbuvir with or without ribavirin has not been established for HCV genotype 3 patients with cirrhosis or for HCV genotype 1 patients with Child-Pugh C cirrhosis [see Clinical Studies (14.2, 14.4)].  

For patients with HCV/HIV-1 coinfection, follow the dosage recommendations in Table 1 [see Clinical Studies (14)]. Refer to Drug Interactions (7) for dosage recommendations for concomitant HIV-1 antiviral drugs.

For specific dosage recommendations for sofosbuvir, refer to the prescribing information.

For HCV genotype 1 or 3 patients with Child-Pugh B or C cirrhosis or post-transplantation patients, the starting dose of ribavirin is 600 mg once daily, increasing up to 1000 mg daily as tolerated. The starting dose and on-treatment dose of ribavirin can be decreased based on hemoglobin and creatinine clearance.

For HCV genotype 3 patients with compensated cirrhosis (Child-Pugh A), the recommended dosing of ribavirin is based on weight (1000 mg for patients weighing less than 75 kg and 1200 mg for those weighing at least 75 kg administered orally in two divided doses with food).

**Table 1: Recommended Treatment Regimen and Duration for Daklinza in Patients with Genotype 1 or 3 HCV**

<table>
<thead>
<tr>
<th>Genotype 1</th>
<th>Patient Population</th>
<th>Treatment and Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without cirrhosis</td>
<td>Daklinza + sofosbuvir for 12 weeks</td>
</tr>
<tr>
<td>Compensated (Child-Pugh A) cirrhosis</td>
<td>Daklinza + sofosbuvir + ribavirin for 12 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post-transplant</td>
<td></td>
</tr>
</tbody>
</table>
**Brand Name**

<table>
<thead>
<tr>
<th>Genotype 3</th>
<th>FDA Recommended Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without cirrhosis</td>
<td>Daklinza + sofosbuvir for 12 weeks</td>
</tr>
<tr>
<td>Compensated (Child-Pugh A) or decompensated (Child-Pugh B or C) cirrhosis</td>
<td>Daklinza + sofosbuvir + ribavirin for 12 weeks</td>
</tr>
<tr>
<td>Post-transplant</td>
<td></td>
</tr>
</tbody>
</table>

**Dosage Modification Due to Drug Interactions**

Refer to the drug interactions and contraindication sections for other drugs before coadministration with Daklinza.

**Table 2: Recommended Daklinza Dosage Modification with CYP3A Inhibitors and Inducers**

<table>
<thead>
<tr>
<th>Concomitant Drugs</th>
<th>Daklinza Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP3A inhibitors and certain HIV antiviral agents [see Drug Interactions (7.3)]</td>
<td>30 mg once daily</td>
</tr>
<tr>
<td>Moderate CYP3A inducers and nevirapine [see Drug Interactions (7.3)]</td>
<td>90 mg once daily</td>
</tr>
<tr>
<td>Strong CYP3A inducers [see Contraindications (4)]</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

Dosage reduction of Daklinza for adverse reactions is not recommended.

**Discontinuation of Therapy**

If sofosbuvir is permanently discontinued in a patient receiving Daklinza with sofosbuvir, then Daklinza should also be discontinued.

**Epclusa**

(sofosbuvir/velpatasvir)

**Testing Prior to the Initiation of Therapy**

Test all patients for evidence of current or prior HBV infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) before initiating HCV treatment with Epclusa [see Warnings and Precautions (5.1)].

**Recommended Dosage**

The recommended dosage of Epclusa is one tablet taken orally once daily with or without food [see Clinical Pharmacology (12.3)]. One tablet of Epclusa contains 400 mg of sofosbuvir and 100 mg of velpatasvir. Table 1 shows the recommended treatment regimen and duration based on patient population.

For patients with HCV/HIV-1 coinfection, follow the dosage recommendations in Table 1 [see Clinical Studies (14.3)]. Refer to Drug Interactions (7) for dosage recommendations for concomitant HIV-1 antiviral drugs.

**Table 1: Recommended Treatment Regimen in Patients with Genotype 1, 2, 3, 4, 5, or 6 HCV**

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Treatment Regimen and Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naive and treatment-experienced&lt;sup&gt;a&lt;/sup&gt; without cirrhosis and with compensated cirrhosis (Child-Pugh A)</td>
<td>Epclusa 12 weeks</td>
</tr>
<tr>
<td>Treatment-naive and treatment-experienced&lt;sup&gt;a&lt;/sup&gt; with decompensated cirrhosis (Child-Pugh B or C)</td>
<td>Epclusa + ribavirin&lt;sup&gt;b&lt;/sup&gt; 12 weeks</td>
</tr>
</tbody>
</table>

<sup>a</sup> In clinical trials, regimens contained peginterferon alfa/ribavirin with or without an HCV NS3/4A protease inhibitor (boceprevir, simeprevir, or telaprevir).

<sup>b</sup> When administered with EPCLUSA, the recommended dosage of ribavirin is based on weight (administered with food): 1000 mg per day for patients less than 75 kg and 1200 mg for those weighing at least 75 kg, divided and administered twice daily. The starting dosage and on-treatment dosage of ribavirin can be decreased based on hemoglobin and creatinine clearance. For ribavirin dosage modifications, refer to the ribavirin prescribing information.

**No Dosage Recommendations in Severe Renal Impairment and End Stage Renal Disease**
<table>
<thead>
<tr>
<th>Brand Name</th>
<th>FDA Recommended Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvoni</td>
<td><strong>Testing Prior to the Initiation of Therapy</strong>&lt;br&gt;Test all patients for evidence of current or prior HBV infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) before initiating HCV treatment with Harvoni [see Warnings and Precautions (5.1)].&lt;br&gt;&lt;br&gt;<strong>Recommended Dosage</strong>&lt;br&gt;The recommended dosage of Harvoni is one tablet taken orally once daily with or without food [see Clinical Pharmacology (12.3)].&lt;br&gt;&lt;br&gt;Relapse rates are affected by baseline host and viral factors and differ between treatment durations for certain subgroups [see Clinical Studies (14)].&lt;br&gt;&lt;br&gt;Table 1 below shows the recommended Harvoni treatment duration based on patient population.&lt;br&gt;&lt;br&gt;Table 1 shows the recommended Harvoni treatment regimen and duration based on patient population.&lt;br&gt;&lt;br&gt;For patients with HCV/HIV-1 co-infection, follow the dosage recommendations in Table 1 [see Clinical Studies (14)]. Refer to the Drug Interactions (7) section [of the prescribing information] for dosage recommendations for concomitant HIV-1 antiviral drugs.</td>
</tr>
</tbody>
</table>

**Table 1 - Recommended Treatment Duration for Harvoni in Patients with Genotype 1, 4, 5 or 6 HCV**

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Treatment Regimen and Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genotype 1</strong></td>
<td></td>
</tr>
<tr>
<td>Treatment-naive without cirrhosis or with compensated cirrhosis (Child-Pugh A)</td>
<td>Harvoni 12 weeks*</td>
</tr>
<tr>
<td>Treatment-experienced** without cirrhosis</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Treatment-experienced** with compensated cirrhosis (Child-Pugh A)</td>
<td>Harvoni 24 weeks†</td>
</tr>
<tr>
<td>Treatment-naive and treatment-experienced** with decompensated cirrhosis (Child-Pugh B or C)</td>
<td>Harvoni + ribavirin‡ 12 weeks</td>
</tr>
<tr>
<td><strong>Genotype 1 or 4</strong></td>
<td></td>
</tr>
<tr>
<td>Treatment-naive and treatment-experienced** liver transplant recipients without cirrhosis, or with compensated cirrhosis (Child-Pugh A)</td>
<td>Harvoni + ribavirin§ 12 weeks</td>
</tr>
<tr>
<td><strong>Genotype 4, 5 or 6</strong></td>
<td></td>
</tr>
<tr>
<td>Treatment-naive and treatment-experienced**, without cirrhosis or with compensated cirrhosis (Child-Pugh A)</td>
<td>Harvoni 12 weeks</td>
</tr>
</tbody>
</table>

* Harvoni for 8 weeks can be considered in treatment-naive genotype 1 patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL [see Clinical Studies (14.2)].
** Treatment-experienced patients include those who have failed treatment with a peginterferon alfa + ribavirin based regimen with or without an HCV protease inhibitor.
† Harvoni + ribavirin for 12 weeks can be considered in treatment-experienced genotype 1 patients with cirrhosis who are eligible for ribavirin [see Clinical Studies (14.2)]. 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 < 75 kg and 1200 mg for those ≥ 75 kg in two divided doses with food. If the starting dosage of ribavirin is not well tolerated, the dosage should be reduced as clinically indicated based on hemoglobin levels.

The daily dosage of ribavirin is weight-based (1000 mg for patients < 75 kg and 1200 mg for those ≥ 75 kg) administered orally in two divided doses with food.

For further information on ribavirin dosing and dosage modifications, refer to the ribavirin prescribing information [see Clinical Studies (14.5)].

**Recommended Dosage in Pediatric Patients 12 Years of Age and Older or Weighing at Least 35 kg**

The recommended dosage of Harvoni in pediatric patients 12 years of age and older or weighing at least 35 kg is one tablet (90 mg ledipasvir and 400 mg sofosbuvir) taken orally once daily with or without food for 12 weeks [see Clinical Pharmacology (12.3) and Clinical Studies (14.6)].

Table 2 shows the recommended HARVONI duration based on pediatric patient population.

For patients with HCV/HIV-1 coinfection, follow the dosage recommendations in Table 2 [see Use in Specific Populations (8.4)]. Refer to Drug Interactions (7) for dosage recommendations for concomitant HIV-1 antiviral drugs.

**Table 2 - 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**

<table>
<thead>
<tr>
<th>Genotype 1</th>
<th>Treatment Regimen and Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naïve without cirrhosis or with compensated cirrhosis (Child-Pugh A)</td>
<td>Harvoni 12 weeks</td>
</tr>
<tr>
<td>Treatment-experienced(^a) without cirrhosis</td>
<td>Harvoni 12 weeks</td>
</tr>
<tr>
<td>Treatment-experienced(^a) with compensated cirrhosis (Child-Pugh A)</td>
<td>Harvoni 24 weeks</td>
</tr>
</tbody>
</table>

Genotype 4, 5, or 6

| Treatment-naïve and treatment-experienced\(^a\) without cirrhosis or with compensated cirrhosis (Child-Pugh A) | Harvoni 12 weeks |

\(^a\) Treatment-experienced patients have failed an interferon based regimen with or without ribavirin.

**Severe Renal Impairment and End Stage Renal Disease**

No dosage recommendation can be given for patients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] less than 30 mL/min/1.73 m\(^2\)) or with end stage renal disease (ESRD) due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

**Mavyret (glecaprevir/pibrentasvir)**

**Testing Prior to the Initiation of Therapy**

Test all patients for evidence of current or prior HBV infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) before initiating HCV treatment with Mavyret [see Warnings and Precautions (5.1)].

**Recommended Dosage in Adults**

Mavyret is a fixed-dose combination product containing glecaprevir 100 mg and pibrentasvir 40 mg in each tablet.

The recommended oral dosage of Mavyret is three tablets (total daily dose: glecaprevir 300 mg and pibrentasvir 120 mg) taken once daily with food [see Clinical Pharmacology (12.3)].

Tables 1 and 2 provide the recommended Mavyret treatment duration based on the patient population in HCV mono-infected and HCV/HIV-1 co-infected patients with compensated liver disease (with or without cirrhosis) and with or without renal impairment including patients receiving dialysis.
### Table 1 – Recommended Duration for Treatment-Naive Patients

<table>
<thead>
<tr>
<th>HCV Genotype</th>
<th>No Cirrhosis</th>
<th>Compensated Cirrhosis (Child-Pugh A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 2, 3, 4, 5, or 6</td>
<td>8 weeks</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

### Table 2 – Recommended Duration for Treatment-Experienced Patients

<table>
<thead>
<tr>
<th>HCV Genotype</th>
<th>Patients Previously Treated With a Regimen Containing:</th>
<th>No Cirrhosis</th>
<th>Compensated Cirrhosis (Child-Pugh A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>An NS5A inhibitor(^1) without prior treatment with an NS3/4A protease inhibitor</td>
<td>16 weeks</td>
<td>16 weeks</td>
</tr>
<tr>
<td></td>
<td>An NS3/4A PI(^2) without prior treatment with an NS5A inhibitor</td>
<td>12 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>1, 2, 4, 5, or 6</td>
<td>PRS(^3)</td>
<td>8 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>3</td>
<td>PRS(^3)</td>
<td>16 weeks</td>
<td>16 weeks</td>
</tr>
</tbody>
</table>

1. In clinical trials, subjects were treated with prior regimens containing ledipasvir and sofosbuvir or daclatasvir with pegylated interferon and ribavirin.
2. In clinical trials, subjects were treated with prior regimens containing simeprevir and sofosbuvir, or simeprevir, boceprevir, or telaprevir with pegylated interferon and ribavirin.
3. PRS=Prior treatment experience with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor.

### Hepatic Impairment

Mavyret is not recommended in patients with moderate hepatic impairment (Child-Pugh B) and is contraindicated in patients with severe hepatic impairment (Child-Pugh C) [see Contraindications (4), Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)].

### Olysio (simeprevir)

#### Testing Prior to Initiation of Therapy

**Testing for HBV infection**

Test all patients for evidence of current or prior HBV infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) before initiating HCV treatment with Olysio [see Warnings and Precautions (5.1)].

**Q80K Testing in HCV Genotype 1a-Infected Patients**

**Olysio in Combination with Sofosbuvir**

In HCV genotype 1a-infected patients with compensated cirrhosis, screening for the presence of virus with the NS3 Q80K polymorphism may be considered prior to initiation of treatment with Olysio with sofosbuvir [see Clinical Studies (14.2)].

**Olysio in Combination with Peg-IFN-alfa and RBV**

Prior to initiation of treatment with Olysio in combination with Peg-IFN-alfa and RBV, screening patients with HCV genotype 1a infection for the presence of virus with the NS3 Q80K polymorphism is strongly recommended and alternative therapy should be considered for patients infected with HCV genotype 1a containing the Q80K polymorphism [see Indications and Usage (1) and Microbiology (12.4)].

**Hepatic Laboratory Testing**

Monitor liver chemistry tests before and during Olysio combination therapy [see Warnings and Precautions (5.3)].

**Olysio Combination Treatment**

Administer Olysio in combination with other antiviral drugs for the treatment of chronic HCV infection. Olysio monotherapy is not recommended. The recommended dosage of Olysio is one 150 mg capsule taken orally once daily with food [see Clinical Pharmacology (12.3)]. The capsule should be swallowed...
FDA Recommended Dosing

As a whole. For specific dosing recommendations for the antiviral drugs used in combination with Olysio, refer to their respective prescribing information.

Olysio can be taken in combination with sofosbuvir or in combination with Peg-IFN-alfa and RBV.

Olysio in Combination with Sofosbuvir

Table 1 displays the recommended treatment regimen and duration of Olysio in combination with sofosbuvir in patients with chronic HCV genotype 1 infection.

Table 1: Recommended Treatment Regimen and Duration for Olysio and Sofosbuvir Combination Therapy in Patients with Chronic HCV Genotype 1 Infection

<table>
<thead>
<tr>
<th>Patient Population (HCV Genotype 1)</th>
<th>Treatment Regimen and Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naive and treatment-experienced* patients:</td>
<td></td>
</tr>
<tr>
<td>without cirrhosis</td>
<td>12 weeks of Olysio + sofosbuvir</td>
</tr>
<tr>
<td>with compensated cirrhosis (Child-Pugh A)</td>
<td>24 weeks of Olysio + sofosbuvir</td>
</tr>
</tbody>
</table>

* Treatment-experienced patients include prior relapsers, prior partial responders and prior null responders who failed prior IFN-based therapy [see Clinical Studies (14)].

Olysio in Combination with Peg-IFN-alfa and RBV

Table 2 displays the recommended treatment regimen and duration of Olysio in combination with Peg-IFN-alfa and RBV in mono-infected and HCV/HIV-1 co-infected patients with HCV genotype 1 or 4 infection. Refer to Table 3 for treatment stopping rules for Olysio combination therapy with Peg-IFN-alfa and RBV.

Table 2: Recommended Treatment Regimen and Duration for OLYSIO, Peg-IFN-alfa, and RBV Combination Therapy in Patients with Chronic HCV Genotype 1 or 4 Infection

<table>
<thead>
<tr>
<th>Patient Population (HCV Genotype 1 or 4)</th>
<th>Treatment Regimen and Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naive patients and prior relapers*:</td>
<td></td>
</tr>
<tr>
<td>HCV mono-infected patients without cirrhosis or with compensated cirrhosis (Child-Pugh A)</td>
<td>12 weeks of Olysio + Peg-IFN-alfa + RBV followed by an additional 12 weeks of Peg-IFN-alfa + RBV (total treatment duration of 24 weeks)†</td>
</tr>
<tr>
<td>HCV/HIV-1 co-infected patients without cirrhosis</td>
<td>12 weeks of Olysio + Peg-IFN-alfa + RBV followed by additional 36 weeks of Peg-IFN-alfa + RBV (total treatment duration of 48 weeks)‡</td>
</tr>
<tr>
<td>HCV/HIV-1 co-infected patients with compensated cirrhosis (Child-Pugh A)</td>
<td>12 weeks of Olysio + Peg-IFN-alfa + RBV followed by additional 36 weeks of Peg-IFN-alfa + RBV (total treatment duration of 48 weeks)‡</td>
</tr>
<tr>
<td>Prior non-responders (including partial‡ and null responders#):</td>
<td></td>
</tr>
<tr>
<td>HCV/HIV-1 co-infected or HCV mono-infected patients without cirrhosis or with compensated cirrhosis (Child-Pugh A)</td>
<td>12 weeks of Olysio + Peg-IFN-alfa + RBV followed by an additional 36 weeks of Peg-IFN-alfa + RBV (total treatment duration of 48 weeks)‡</td>
</tr>
</tbody>
</table>

† Recommended duration of treatment if patient does not meet stopping rules (see Table 3).
‡ Prior partial responder: prior on-treatment ≥ 2 log₁₀ IU/mL reduction in HCV RNA from baseline at Week 12 and HCV RNA detected at end of prior IFN-based therapy [see Clinical Studies (14)].
# Prior null responder: prior on-treatment < 2 log₁₀ IU/mL reduction in HCV RNA from baseline at Week 12 during prior IFN-based therapy [see Clinical Studies (14)].

HIV = human immunodeficiency virus.

Discontinuation of Dosing

Olysio in Combination with Sofosbuvir

No treatment stopping rules apply to the combination of Olysio with sofosbuvir [see Clinical Studies (14)].

Olysio in Combination with Peg-IFN-alfa and RBV
During treatment, HCV RNA levels should be monitored as clinically indicated using a sensitive assay with a lower limit of quantification of at least 25 IU/mL. Because patients with an inadequate on-treatment virologic response (i.e., HCV RNA greater or equal to 25 IU/mL) are not likely to achieve a sustained virologic response (SVR), discontinuation of treatment is recommended in these patients. Table 3 presents treatment stopping rules for patients who experience an inadequate on-treatment virologic response at Weeks 4, 12, and 24.

Table 3: Treatment Stopping Rules in Patients Receiving Olysio in Combination with Peg-IFN-alfa and RBV with Inadequate On-Treatment Virologic Response

<table>
<thead>
<tr>
<th>Treatment Week</th>
<th>HCV RNA</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>&gt; 25 IU/mL</td>
<td>Discontinue Olysio, Peg-IFN-alfa, and RBV</td>
</tr>
<tr>
<td>Week 12</td>
<td></td>
<td>Discontinue Peg-IFN-alfa, and RBV (treatment with Olysio is complete at Week 12)</td>
</tr>
<tr>
<td>Week 24</td>
<td></td>
<td>Discontinue Peg-IFN-alfa, and RBV (treatment with Olysio is complete at Week 12)</td>
</tr>
</tbody>
</table>

Dosage Adjustment or Interruption
To prevent treatment failure, avoid reducing the dosage of Olysio or interrupting treatment. If treatment with Olysio is discontinued because of adverse reactions or inadequate on-treatment virologic response, Olysio treatment must not be reinitiated [see Warnings and Precautions (5.3)].

If adverse reactions potentially related to the antiviral drug(s) used in combination with Olysio occur, refer to the instructions outlined in their respective prescribing information for recommendations on dosage adjustment or interruption.

If any of the other antiviral drugs used in combination with Olysio for the treatment of CHC infection are permanently discontinued for any reason, Olysio should also be discontinued.

Not Recommended in Patients with Moderate or Severe Hepatic Impairment
Olysio is not recommended for patients with moderate or severe hepatic impairment (Child-Pugh B or C) [see Warnings and Precautions (5.3), Adverse Reactions (6.1), Use in Specific Populations (8.8), and Clinical Pharmacology (12.3)].

Sovaldi (sofosbuvir)

Testing Prior to the Initiation of Therapy
Test all patients for evidence of current or prior HBV infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) before initiating HCV treatment with Sovaldi [see Warnings and Precautions (5.1)].

Recommended Dosage
The recommended dosage of Sovaldi is one 400 mg tablet, taken orally, once daily with or without food. [see Clinical Pharmacology (12.3)].

Administer Sovaldi in combination with ribavirin or in combination with pegylated interferon and ribavirin for the treatment of HCV. The recommended treatment regimen and duration for Sovaldi combination therapy is provided in Table 1.

For patients with HCV/HIV-1 co-infection, follow the dosage recommendations in Table 1. Refer to Drug Interactions (7) for dosage recommendations for concomitant HIV-1 antiviral drugs.

Table 1 - Recommended Treatment Regimen and Duration in Adult Patients with Genotype 1, 2, 3, or 4 HCV

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Treatment Regimen and Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1 or 4</td>
<td>Treatment-naive without cirrhosis or with compensated cirrhosis (Child-Pugh A) Sovaldi + peginterferon alfa² + ribavirin³ 12 weeks</td>
</tr>
<tr>
<td>Brand Name</td>
<td>FDA Recommended Dosing</td>
</tr>
<tr>
<td>------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Genotype 2</td>
<td>Treatment-naïve and treatment-experienced&lt;sup&gt;a&lt;/sup&gt; without cirrhosis or with compensated cirrhosis (Child-Pugh A)</td>
</tr>
<tr>
<td>Genotype 3</td>
<td>Treatment-naïve and treatment-experienced&lt;sup&gt;a&lt;/sup&gt; without cirrhosis or with compensated cirrhosis (Child-Pugh A)</td>
</tr>
</tbody>
</table>

<sup>a</sup> See peginterferon alfa prescribing information for dosage recommendation for patients with genotype 1 or 4 HCV.

<sup>b</sup> Dosage of ribavirin is weight-based (<75 kg = 1000 mg and ≥75 kg = 1200 mg). The daily dosage of ribavirin is administered orally in two divided doses with food. Patients with renal impairment (CrCl ≤50 mL/min) require ribavirin dosage reduction; refer to ribavirin prescribing information.

<sup>c</sup> Treatment-experienced patients have failed an interferon-based regimen with or without ribavirin.

**Patients with Genotype 1 HCV Who are Ineligible to Receive an Interferon-Based Regimen**

Sovaldi in combination with ribavirin for 24 weeks can be considered as a therapeutic option for patients with genotype 1 infection who are ineligible to receive an interferon-based regimen [see Clinical Studies (14.4)]. Treatment decision should be guided by an assessment of the potential benefits and risks for the individual patient.

**Patients with Hepatocellular Carcinoma Awaiting Liver Transplantation**

Administer Sovaldi in combination with ribavirin for up to 48 weeks or until the time of liver transplantation, whichever occurs first, to prevent post-transplant HCV reinfection [see Use in Specific Populations (8.8)].

**Recommended Dosage in Pediatric Patients 12 Years of Age and Older or Weighing at Least 35 kg**

The recommended dosage of Sovaldi in pediatric patients 12 years of age and older or weighing at least 35 kg is one 400 mg tablet taken orally once daily with or without food in combination with ribavirin [see Clinical Pharmacology (12.3) and Clinical Studies (14.5)].

The recommended treatment regimen and duration for SOVALDI combination therapy is provided in Table 2. Table 3 provides the weight-based dosage of ribavirin when used in combination with Sovaldi for pediatric patients. For patients with HCV/HIV-1 coinfection, follow the dosage recommendations in Table 2 and Table 3. Refer to Drug Interactions (7) for dosage recommendations for concomitant HIV-1 antiviral drugs.

**Table 2 – Recommended Treatment Regimen and Duration in Pediatric Patients 12 Years of Age and Older or Weighing at Least 35 kg**

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Treatment Regimen and Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 2</td>
<td>Sovaldi + ribavirin&lt;sup&gt;b&lt;/sup&gt; 12 weeks</td>
</tr>
<tr>
<td>Genotype 3</td>
<td>Sovaldi + ribavirin&lt;sup&gt;b&lt;/sup&gt; 24 weeks</td>
</tr>
</tbody>
</table>

<sup>a</sup> Treatment-experienced patients have failed an interferon-based regimen with or without ribavirin.

<sup>b</sup> See Table 3 for weight-based ribavirin dosing recommendations.

**Table 3 – Recommended Dosing for Ribavirin in Combination Therapy with Sovaldi for Pediatric Patients 12 Years of Age and Older or Weighing at Least 35 kg**

<table>
<thead>
<tr>
<th>Body Weight kg</th>
<th>Ribavirin Daily Dosage&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>less than 47</td>
<td>15 mg/kg/day</td>
</tr>
<tr>
<td>Brand Name</td>
<td>FDA Recommended Dosing</td>
</tr>
<tr>
<td>------------</td>
<td>------------------------</td>
</tr>
<tr>
<td></td>
<td>47-49</td>
</tr>
<tr>
<td></td>
<td>50-65</td>
</tr>
<tr>
<td></td>
<td>66-80</td>
</tr>
<tr>
<td></td>
<td>greater than 80</td>
</tr>
</tbody>
</table>

a. The daily dosage of ribavirin is weight-based and is administered orally in two divided doses with food.

**Dosage Modification**

Dosage reduction of Sovaldi is not recommended.

If a patient has a serious adverse reaction potentially related to peginterferon alfa and/or ribavirin, the peginterferon alfa and/or ribavirin dosage should be reduced or discontinued, if appropriate, until the adverse reaction abates or decreases in severity. Refer to the peginterferon alfa and ribavirin prescribing information for additional information about how to reduce and/or discontinue the peginterferon alfa and/or ribavirin dosage.

**Discontinuation of Dosing**

If the other agents used in combination with Sovaldi are permanently discontinued, Sovaldi should also be discontinued.

**Severe Renal Impairment and End Stage Renal Disease**

No dosage recommendation can be given for patients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] less than 30 mL/min/1.73m²) or with end stage renal disease (ESRD) due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

**Technivie**

(ombitasvir/paritaprevir/ritonavir)

**Testing Prior to Initiation of Technivie**

- Test all patients for evidence of current or prior HBV infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) before initiating HCV treatment with Technivie [see Warnings and Precautions (5.1)].
- Prior to initiation of Technivie, assess hepatic laboratory and clinical evidence of hepatic decompensation. Prior to initiation of ribavirin, assess for underlying cardiac disease and refer to the ribavirin prescribing information [see Contraindications (4) and Warnings and Precautions (5.1 and 5.2)].

**Recommended Dosage in Adults**

Technivie is ombitasvir, paritaprevir and ritonavir fixed dose combination tablets.

The recommended dosage of Technivie is two tablets taken orally once daily (in the morning). Take Technivie with a meal without regard to fat or calorie content [see Clinical Pharmacology].

Technivie is used in combination with ribavirin (RBV). When administered with Technivie, the recommended dosage of RBV is based on weight: 1000 mg per day for subjects less than 75 kg and 1200 mg per day for those weighing at least 75 kg, divided and administered twice-daily with food. For ribavirin dosage modifications, refer to the ribavirin prescribing information.

Table 1 shows the recommended Technivie treatment regimen and duration for HCV genotype 4 patients without cirrhosis or with compensated cirrhosis.

**Table 1. Treatment Regimen and Duration for Patients with HCV Genotype 4 without Cirrhosis or with Compensated Cirrhosis**

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 4 without cirrhosis or with compensated cirrhosis (Child-Pugh A)</td>
<td>Technivie + ribavirin*</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>
**Brand Name** | **FDA Recommended Dosing**<br>* Technivie administered without RBV for 12 weeks may be considered for treatment-naïve patients without cirrhosis who cannot take or tolerate ribavirin [see Microbiology (12.4) and Clinical Studies (14)].

---

**Dosage in Patients with Hepatic Impairment**
Technivie is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C) [see Contraindications (4), Warnings and Precautions (5.2), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)].

| Viekira Pak/ Viekira XR (ombitasvir/ paritaprevir/ ritonavir and dasabuvir) | **Testing Prior to Initiation of Viekira Pak/Viekira XR**<br>• Test all patients for evidence of current or prior HBV infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) before initiating HCV treatment with Viekira Pak/Viekira XR [see Warnings and Precautions (5.1)].<br>• Prior to initiation of Viekira Pak/Viekira XR, assess for laboratory and clinical evidence of hepatic decompensation [see Warnings and Precautions (5.2 and 5.3)].

| Viekira Pak – Recommended Dosage in Adults | **Viekira Pak** is ombitasvir, paritaprevir, ritonavir fixed dose combination tablets copackaged with dasabuvir tablets.

The recommended oral dosage of Viekira Pak is two ombitasvir, paritaprevir, ritonavir tablets once daily (in the morning) and one dasabuvir tablet twice daily (morning and evening). Take Viekira Pak with a meal without regard to fat or calorie content [see Clinical Pharmacology].

Viekira Pak is used in combination with ribavirin (RBV) in certain patient populations (see Table 1). When administered with Viekira Pak, the recommended dosage of RBV is based on weight: 1000 mg/day for subjects < 75 kg and 1200 mg/day for those ≥75 kg, divided and administered twice-daily with food. For ribavirin dosage modifications, refer to the ribavirin prescribing information.

For patients with HCV/HIV-1 co-infection, follow the dosage recommendations in Table 1. Refer to Drug Interactions [section of the prescribing information] for dosage recommendations for concomitant HIV-1 antiviral drugs.

Table 1 shows the recommended Viekira Pak treatment regimen and duration based on patient population.

| **Table 1. Treatment Regimen and Duration by Patient Population** (Treatment-Naïve or Interferon-Experienced) | **Patient Population** | **Treatment**<br>Viekira Pak + ribavirin | **Duration**<br>12 weeks | **Genotype 1a, without cirrhosis**<br>Viekira Pak + ribavirin | **24 weeks**<br>Genotype 1a, with compensated cirrhosis (Child-Pugh A) | **Viekira Pak** | **12 weeks**<br>Genotype 1b, with or without compensated cirrhosis (Child-Pugh A)

* Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.<br>**Viekira Pak administered with ribavirin for 12 weeks may be considered for some patients based on prior treatment history [see Clinical Studies].

**Use in Liver Transplant Recipients**
In liver transplant recipients with normal hepatic function and mild fibrosis (Metavir fibrosis score 2 or lower), the recommended duration of Viekira Pak with ribavirin is 24 weeks, irrespective of HCV genotype 1 subtype [see Clinical Studies]. When Viekira Pak is administered with calcineurin inhibitors in liver transplant recipients, dosage adjustment of calcineurin inhibitors is needed [see Drug Interactions].
**Brand Name** | **FDA Recommended Dosing**
--- | ---
**Hepatic Impairment** | Viekira Pak is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C) [see Contraindications, Warnings and Precautions, Use in Specific Populations, and Clinical Pharmacology].

**Viekira XR – Recommended Dosage in Adults** | Viekira XR is a 4-drug fixed-dose combination, extended-release tablet containing 200 mg of dasabuvir, 8.33 mg of ombitasvir, 50 mg of paritaprevir, and 33.33 mg of ritonavir.

The recommended dosage of Viekira XR is three tablets taken orally once daily.
- Viekira XR must be taken with a meal because administration under fasting conditions may result in reduced virologic response and possible development of resistance [see Clinical Pharmacology (12.3)].
- Swallow tablets whole. Splitting, crushing, or chewing tablets may compromise the extended-release performance, efficacy, and/or safety of Viekira XR.
- For optimal release of dasabuvir, alcohol should not be consumed within 4 hours of taking Viekira XR.

Viekira XR is used in combination with ribavirin (RBV) in certain patient populations (see Table 1). When administered with Viekira XR, the recommended dosage of RBV is based on weight: 1000 mg/day for subjects <75 kg and 1200 mg/day for those ≥75 kg, divided and administered twice-daily with food. The starting dosage and on-treatment dosage of RBV can be decreased based on changes in hemoglobin levels and/or creatinine clearance. For ribavirin dosage modifications, refer to the ribavirin prescribing information.

For patients with HCV/HIV-1 co-infection, follow the dosage recommendations in Table 1. Refer to Drug Interactions (7) for dosage recommendations for concomitant HIV-1 antiviral drugs.

Table 1 shows the recommended Viekira XR treatment regimen and duration based on patient population.

**Table 1. Treatment Regimen and Duration by Patient Population (Treatment-Naive or Interferon-Experienced)**

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Treatment*</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1a, without cirrhosis</td>
<td>Viekira XR + ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 1a, with compensated cirrhosis (Child-Pugh A)</td>
<td>Viekira XR + ribavirin</td>
<td>24 weeks**</td>
</tr>
<tr>
<td>Genotype 1b, with or without compensated cirrhosis (Child-Pugh A)</td>
<td>Viekira XR</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

* Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.

**Viekira Pak administered with ribavirin for 12 weeks may be considered for some patients based on prior treatment history [see Clinical Studies].

**Use in Liver Transplant Recipients**
In liver transplant recipients with normal hepatic function and mild fibrosis (Metavir fibrosis score 2 or lower), the recommended duration of Viekira XR with ribavirin is 24 weeks, irrespective of HCV genotype 1 subtype [see Clinical Studies (14.6)]. When Viekira XR is administered with calcineurin inhibitors in liver transplant recipients, dosage adjustment of calcineurin inhibitors is needed [see Drug Interactions (7)].

**Hepatic Impairment**
Viekira XR is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C) [see Contraindications (4), Warnings and Precautions (5.1), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)].
<table>
<thead>
<tr>
<th>Brand Name</th>
<th>FDA Recommended Dosing</th>
</tr>
</thead>
</table>
| **Vosevi**
(sofosbuvir/
velpatasvir/
voxilaprevir) | **Testing Prior to the Initiation of Therapy**<br>Test all patients for evidence of current or prior HBV infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) before initiating HCV treatment with Vosevi [see Warnings and Precautions (5.1)].<br>**Recommended Dosage**<br>The recommended dosage of Vosevi is one tablet, taken orally, once daily with food [see Clinical Pharmacology (12.3)]. One tablet of Vosevi contains 400 mg of sofosbuvir, 100 mg of velpatasvir, and 100 mg of voxilaprevir. Table 1 shows the recommended treatment regimen and duration based on patient population.<br>**Table 1 – Recommended Treatment Regimen and Duration in Adults Without Cirrhosis or With Compensated Cirrhosis (Child-Pugh A)**<br>![Table](attachment://table1.png)<br>a. In clinical trials, prior NS5A inhibitor experience included daclatasvir, elbasvir, ledipasvir, ombitasvir, or velpatasvir.<br>b. In clinical trials, prior treatment experience included sofosbuvir with or without any of the following: peginterferon alfa/ribavirin, ribavirin, HCV NS3/4A protease inhibitor (boceprevir, simeprevir or telaprevir).<br>**No Dosage Recommendations in Severe Renal Impairment and End Stage Renal Disease**<br>No dosage recommendation can be given for patients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] less than 30 mL/min/1.73 m²) or with end stage renal disease (ESRD), due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].<br>**Moderate or Severe Hepatic Impairment**<br>Vosevi is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C) due to higher exposures of voxilaprevir in these patients [see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]. |
| **Zepatier**
(elbasvir/
grazoprevir) | **Testing Prior to the Initiation of Therapy**<br>Testing for HBV Infection<br>Test all patients for evidence of current or prior HBV infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) before initiating HCV treatment with Zepatier [see Warnings and Precautions (5.1)].<br>**NS5A Resistance Testing in HCV Genotype 1a-Infected Patients**<br>Testing patients with HCV genotype 1a infection for the presence of virus with NS5A resistance-associated polymorphisms is recommended prior to initiation of treatment with Zepatier to determine dosage regimen and duration [see Dosage and Administration (2.2)], Table 1. In subjects receiving Zepatier for 12 weeks, sustained virologic response (SVR12) rates were lower in genotype 1a-infected patients with one or more baseline NS5A resistance-associated polymorphisms at amino acid positions 28, 30, 31, or 93 [see Microbiology (12.4)], Table 11.<br>**Hepatic Laboratory Testing**<br>Obtain hepatic laboratory testing prior to and during treatment with Zepatier [see Warnings and Precautions (5.1)].<br>**Recommended Dosage in Adults**<br>Zepatier is a two-drug, fixed-dose combination product containing 50 mg of elbasvir and 100 mg of grazoprevir in a single tablet. The recommended dosage of Zepatier is one tablet taken orally once daily with or without food [see Clinical Pharmacology (12.3)]. Zepatier is used in combination with ribavirin in certain patient populations (see Table 1). When administered with Zepatier, the recommended dosage of ribavirin in patients without renal impairment is weight-based administered.
FDA Recommended Dosing

in two divided doses with food. For further information on ribavirin dosing and dosage modifications, refer to the ribavirin prescribing information.

Treatment Regimen and Duration of Therapy

Relapse rates are affected by baseline host and viral factors and differ between treatment regimens and durations for certain subgroups [see Clinical Studies (14)].

Table 1 below provides the recommended Zepatier treatment regimen and duration based on the patient population and genotype in HCV mono-infected and HCV/HIV-1 co-infected patients with or without cirrhosis and with or without renal impairment including patients receiving hemodialysis.

Table 1: Recommended Dosage Regimens and Durations for Zepatier for Treatment of HCV Genotype 1 or 4 in Patients with or without Cirrhosis

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced* without baseline NS5A polymorphisms†</td>
<td>Zepatier</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced* with baseline NS5A polymorphisms†</td>
<td>Zepatier + RBV‡</td>
<td>16 weeks</td>
</tr>
<tr>
<td>Genotype 1b: Treatment-naïve or PegIFN/RBV-experienced*</td>
<td>Zepatier</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 1a§ or 1b: PegIFN/RBV/PI-experienced¶</td>
<td>Zepatier + RBV‡</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 4: Treatment-naïve</td>
<td>Zepatier</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 4: PegIFN/RBV-experienced*</td>
<td>Zepatier + RBV‡</td>
<td>16 weeks</td>
</tr>
</tbody>
</table>

*Patients who have failed treatment with peginterferon alfa (PegIFN) + ribavirin (RBV).
†NS5A resistance-associated polymorphisms at amino acid positions 28, 30, 31, or 93. See section 2.1 Testing prior to the initiation of therapy, subsection NS5A resistance testing in HCV genotype 1a-infected patients.
‡ For patients with CrCl greater than 50 mL per minute, the recommended dosage of ribavirin is weight-based (less than 66 kg = 800 mg per day, 66 to 80 kg = 1000 mg per day, 81 to 105 kg = 1200 mg per day, greater than 105 kg = 1400 mg per day) administered in two divided doses with food. For patients with CrCl less than or equal to 50 mL per minute, including patients receiving hemodialysis, refer to the ribavirin tablet prescribing information for the correct ribavirin dosage.
§The optimal Zepatier-based treatment regimen and duration of therapy for PegIFN/RBV/PI-experienced genotype 1a-infected patients with one or more baseline NS5A resistance-associated polymorphisms at positions 28, 30, 31, and 93 has not been established.
¶Patients who have failed treatment with PegIFN + RBV + HCV NS3/4A protease inhibitor (PI): boceprevir, simeprevir, or telaprevir

Renal Impairment

No dosage adjustment of Zepatier is recommended in patients with any degree of renal impairment including patients on hemodialysis. Administer Zepatier with or without ribavirin according to the recommendations in Table 1 [see Use in Specific Populations (8.8) and Clinical Studies (14.4)]. Refer to the ribavirin tablet prescribing information for the correct ribavirin dosage for patients with CrCl less than or equal to 50 mL per minute.

Hepatic Impairment

No dosage adjustment of Zepatier is recommended in patients with mild hepatic impairment (Child-Pugh A). Zepatier is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C) [see Contraindications (4), Use in Specific Populations (8.9), and Clinical Pharmacology (12.3)].

Interferon Therapy

| Intron A (interferon alfa-2b) | Chronic Hepatitis C | The recommended dose of Intron A for the treatment of chronic hepatitis C is 3 million IU three times per week (TIW) administered subcutaneously or intramuscularly. In patients tolerating therapy with normalization of ALT at 16 weeks of treatment, Intron A therapy should be extended to 18 to 24 months (72 to 96 weeks) at 3 million IU TIW to improve the sustained response rate (see Clinical |
Pharmacology, Chronic Hepatitis C). Patients who do not normalize their ALTs or have persistently high levels of HCV RNA after 16 weeks of therapy rarely achieve a sustained response with extension of treatment. Consideration should be given to discontinuing these patients from therapy.

When Intron A is administered in combination with Rebetol® (ribavirin), patients with impaired renal function and/or those over the age of 50 should be carefully monitored with respect to the development of anemia. See Rebetol prescribing information for dosing when used in combination with Rebetol for adults and pediatric patients.

Dosage Forms for This Indication

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Concentration</th>
<th>Route</th>
<th>Fixed Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solution 18 MIU multidose</td>
<td>6 MIU/mL</td>
<td>IM, SC</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Dose Adjustment:** If severe adverse reactions develop during Intron A treatment, the dose should be modified (50% reduction) or therapy should be temporarily discontinued until the adverse reactions abate. If intolerance persists after dose adjustment, Intron A therapy should be discontinued.

Pegasys (peginterferon alfa-2a)

**Dosage Overview**

Administer Pegasys by subcutaneous injection once weekly in the abdomen or thigh for the treatment of:
- Adult patients with chronic hepatitis C (CHC) without or with HIV coinfection; and
- Pediatric patients with CHC; and
- Adult patients with chronic hepatitis B (CHB).

For treatment of CHC, use Pegasys in combination with other HCV antiviral drugs. For information about the recommended dosage and administration and the safe and effective use of these other HCV antiviral drugs, refer to their prescribing information. Pegasys monotherapy is only indicated in the treatment of CHC if there are contraindications to or significant intolerance to other HCV antiviral drugs.

For dosage modifications in patients with CHC or CHB:
- Due to neutropenia, thrombocytopenia, ALT elevation, and depression.
- In patients with severe renal impairment (creatinine clearance less than 30 mL/minute) and in patients with creatinine clearance between 30 and 50 mL/minute.

For important administration instructions for all the PEGASYS injection presentations (i.e., vial, prefilled syringe, autoinjector).

**Adult Patients with Chronic Hepatitis C**

**Dosage in Adults with CHC without HIV Coinfection**

Table 1 displays the recommended dosage and duration of Pegasys and other HCV antiviral drugs in adults with CHC (without HIV coinfection) based on HCV genotype.

For treatment of HCV genotype 1 with Pegasys in combination with ribavirin or alone, discontinuation of treatment is recommended if at least a 2 log10 reduction from baseline in HCV RNA has not been demonstrated by 12 weeks of therapy or if undetectable HCV RNA has not been achieved after 24 weeks of therapy. Refer to the prescribing information for specific HCV antiviral drugs used in combination with Pegasys for information on stopping therapy based on treatment response.

Immediately discontinue Pegasys for hepatic decompensation (Child-Pugh score greater than 6 [class B and C]).

**Table 1 – Recommended Adult Dosage for Pegasys for CHC Infection**

<table>
<thead>
<tr>
<th>Hepatitis C Virus Genotype</th>
<th>Pegasys Dosage</th>
<th>Pegasys Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotypes 1, 4*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Brand Name | FDA Recommended Dosing
---|---
**Genotypes 2, 3** | 180 mcg subcutaneous injection in thigh or abdomen once weekly | Refer to the prescribing information of HCV antiviral drugs

**Genotypes 5, 6** | There is insufficient data for dosage recommendations

* If Pegasys is used in combination with other antiviral drugs for CHC, refer to the prescribing information of the other HCV antiviral drugs for the recommended dosage of the other HCV antiviral drugs and duration of the entire treatment regimen.

* If Pegasys and ribavirin are used without other HCV antiviral drugs the recommended duration of therapy is 48 weeks.

** If Pegasys and ribavirin are used without other HCV antiviral drugs the recommended duration of therapy is 24 weeks.

If Pegasys monotherapy is used for treatment of CHC, the recommended Pegasys dosage is 180 mcg via subcutaneous injection in thigh or abdomen once weekly for 48 weeks.

**Dosage in Adults with CHC with HIV Coinfection**
The recommended Pegasys dosage in adults with CHC and HIV coinfection is 180 mcg subcutaneously once weekly in the thigh or abdomen. If Pegasys is used in combination with other antiviral drugs, refer to the prescribing information of the other HCV antiviral drugs for the recommended dosage of the other HCV antiviral drugs and duration of the entire treatment regimen (including Pegasys). If Pegasys and ribavirin are used without other HCV antiviral drugs, the recommended duration of therapy is 48 weeks (regardless of HCV genotype).

**Pediatric Patients with CHC**
Pegasys is administered as 180 mcg/1.73 m² x BSA subcutaneously once weekly, to a maximum dose of 180 mcg, and should be given in combination with ribavirin. The recommended treatment duration for patients with genotype 2 or 3 is 24 weeks and for other genotypes is 48 weeks. Patients who initiate treatment prior to their 18th birthday should maintain the recommended pediatric dosage (not the adult dosage) through the completion of therapy. Refer to the prescribing information of ribavirin for the recommended dosage and duration.

**Adults with Chronic Hepatitis B (CHB)**
The recommended Pegasys dosage in adults with CHB is 180 mcg subcutaneously once weekly in the thigh or abdomen for 48 weeks.

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**PegIntron (peginterferon alfa-2b)**

**Refer to the prescribing information (product label) for complete dosing information. The following is from the “Highlights of Prescribing Information” section of the product label.**

- PegIntron is administered by subcutaneous injection.

<table>
<thead>
<tr>
<th>PegIntron Dose (Adults)*</th>
<th>PegIntron Dose (Pediatric Patients)</th>
<th>Rebetol Dose* (Adults)</th>
<th>Rebetol Dose* (Pediatric Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PegIntron Combination Therapy</td>
<td>1.5 mcg/kg/week</td>
<td>60 mcg/m²/week</td>
<td>800-1400 mg orally daily with food</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15 mg/kg/day orally with food in 2 divided doses</td>
</tr>
</tbody>
</table>

* Refer to Tables 1-7 of the Full Prescribing Information

- Dose reduction is recommended in patients experiencing certain adverse reactions or renal dysfunction.

---

**Drug Availability**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Drug Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral Direct-Acting Antivirals</strong></td>
<td></td>
</tr>
<tr>
<td>Daklinza (daclatasvir)</td>
<td>Available as a 30 mg tablet of daclatasvir (equivalent to 33 mg daclatasvir dihydrochloride) and a 60 mg tablet of daclatasvir (equivalent to 66 mg daclatasvir dihydrochloride) packaged in bottles of 28 tablets.</td>
</tr>
<tr>
<td>Epclusa (sofosbuvir/velpatasvir)</td>
<td>Each tablet contains 400 mg of sofosbuvir and 100 mg of velpatasvir and is packaged in 28-count bottles. Must be dispensed in original container.</td>
</tr>
<tr>
<td>Brand Name</td>
<td>Drug Availability</td>
</tr>
<tr>
<td>----------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Haravoni</strong> (ledipasvir/</td>
<td>Each tablet contains 90 mg ledipasvir and 400 mg sofosbuvir and is packaged in 28-count bottles. Must be dispensed in original container.</td>
</tr>
<tr>
<td>sofosbuvir)</td>
<td></td>
</tr>
<tr>
<td><strong>Mavyret</strong> (glecaprevir/</td>
<td>Each tablet contains 100 mg of glecaprevir and 40 mg of pibrentasvir and is dispensed in a 4-week (monthly) or an 8-week carton. Each weekly carton contains seven daily dose wallets. Each monthly carton contains four weekly cartons. Each 8-week carton contains 2 monthly cartons.</td>
</tr>
<tr>
<td>pibrentasvir)</td>
<td></td>
</tr>
<tr>
<td><strong>Olysio</strong> (simeprevir)</td>
<td>Supplied as 150mg capsules packaged in bottles containing either 28 capsules or 7 capsules (emergency supply). Store Olysio capsules in the original bottle in order to protect from light.</td>
</tr>
<tr>
<td><strong>Sovaldi</strong> (sofosbuvir)</td>
<td>Supplied as 400mg tablets packaged in 28-count bottles. Must be dispensed in original container.</td>
</tr>
<tr>
<td><strong>Technivie</strong> (ombitasvir/</td>
<td>Each tablet contains 12.5 mg ombitasvir, 75 mg paritaprevir and 50 mg ritonavir packaged in a monthly carton for a total of 28 days of therapy. Each monthly carton contains four weekly cartons. Each weekly carton contains seven daily dose packs. Each child resistant daily dose pack contains two Technivie tablets.</td>
</tr>
<tr>
<td>paritaprevir/ ritonavir)</td>
<td></td>
</tr>
<tr>
<td><strong>Viekira Pak</strong>/</td>
<td>Viekira Pak and Viekira XR are dispensed in a monthly carton for a total of 28 days of therapy. Each monthly carton contains four weekly cartons. Each weekly carton contains seven daily dose packs. Each child-resistant daily dose pack contains four tablets: two 12.5/75/50 mg ombitasvir, paritaprevir, ritonavir tablets and two 250 mg dasabuvir tablets, and indicates which tablets need to be taken in the morning and evening.</td>
</tr>
<tr>
<td>Viekira XR (ombitasvir/</td>
<td>Viekira XR: Each child-resistant daily dose pack contains three tablets.</td>
</tr>
<tr>
<td>paritaprevir/ ritonavir and</td>
<td></td>
</tr>
<tr>
<td>dasabuvir)</td>
<td></td>
</tr>
<tr>
<td><strong>Vosevi</strong> (sofosbuvir/</td>
<td>Each tablet contains 400 mg of sofosbuvir, 100 mg of velpatasvir, and 100 mg of voxilaprevir packaged in bottles of 28 tablets. Must be dispensed in original container.</td>
</tr>
<tr>
<td>velpatasvir/ voxilaprevir)</td>
<td></td>
</tr>
<tr>
<td><strong>Zepatier</strong> (elbasvir/</td>
<td>Supplied as tablets, each containing 50 mg elbasvir and 100 mg grazoprevir, packaged into a carton containing two 14-count child-resistant dose packs for a total of 28 tablets.</td>
</tr>
<tr>
<td>grazoprevir)</td>
<td></td>
</tr>
</tbody>
</table>

**Interferon Therapy**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Drug Availability</th>
</tr>
</thead>
</table>
| **Intron A** (interferon alfa-2b) | - Single-use vials of powder for injection with diluent: 10 million IU per vial, 18 million IU per vial, and 50 million IU per vial  
| **Pegasys** (peginterferon alfa-2a) | - Single-use vials containing 180 mcg per 1 mL solution.  
| **PegIntron** (peginterferon alfa-2b) | - Single-use, prefilled syringes containing 180 mcg per 0.5 mL available as a single prefilled syringe and a convenience pack of 4 syringes.  
| **Pegasys** (peginterferon alfa-2a) | - Single-use, autoinjectors containing 180 mcg per 0.5 mL or 135 mcg per 0.5 mL. Both strengths are available as a single prefilled autoinjector or a convenience pack of 4 autoinjectors.  
| **PegIntron** (peginterferon alfa-2b) | - Injection: 50 mcg per 0.5 mL, 80 mcg per 0.5 mL, 120 mcg per 0.5 mL, 150 mcg per 0.5 mL in single-use vial (with 5 mL diluent) and single-use pre-filled pens |

**General Background**

**Disease Overview**

Chronic HCV infection is the most common cause of liver transplantation in the United States and was responsible for more than 19,000 deaths in 2014. (CDC, 2017) Hepatitis C infection begins as acute viral hepatitis, which is usually asymptomatic. Seventy-five percent to 85% of patients develop chronic HCV after acute infection, while the remaining 15% to 25% clear the virus spontaneously. (CDC, 2017) The Centers for Disease Control and Prevention (CDC) estimates that approximately 2.7-3.9 million Americans have chronic HCV infection. (CDC, 2017) Approximately 60% to 70% of patients with chronic HCV will develop chronic liver disease, 5% to 20% will develop cirrhosis over the next 2 to 3 decades, and up to 5% will die from liver cancer (e.g., hepatocellular carcinoma) or cirrhosis. (CDC, 2017)
Hepatitis C virus is a single-stranded RNA virus and a member of the Flaviviridae family. (Crawford, 2009; Deming, 2011) Upon exposure to the host, the virus enters hepatocytes and begins replication of its genome, which codes for a single polyprotein. (Crawford, 2009; Deming, 2011) GT-1 is the most common genotype in the US and is most resistant to treatment. (Deming, 2011) GT-2 and 3 are the next most common genotypes. (Deming, 2011) GT-3 infections progress more rapidly through fibrosis stages than other genotypes. (AASLD/IDSA, 2017) Although the acute infection is frequently asymptomatic, both the innate and acquired immune systems launch an active attack against the virus. (O’Leary, 2010) The extent and intensity of the initial T-cell response appears to be critical in determining whether the acute infection resolves or chronic HCV develops. (O’Leary, 2010) Liver damage from chronic HCV infection is likely autoimmune in nature. (O’Leary, 2010)

Genotype testing is recommended for all infected patients prior to beginning drug treatment. Viral genotyping is used to determine treatment duration, appropriate treatment regimens, and to predict patient response. (Ghany, 2009; Ghany, 2011) Viral genotype does not change during the course of infection. Resistance-associated substitutions, such as amino acid substitutions at positions 28, 30, 31, or 94 of HCV nonstructural protein (NS) 5A and the Q80K polymorphism in HCV NS3/4A, can reduce the efficacy of some direct-acting antiviral agents in certain patient groups. (AASLD/IDSA, 2017) Guidelines recommend screening for RASs depending on the genotype and subtype (for example: genotype 1a and genotype 3) and the regimen being considered. (AASLD/IDSA, 2017) Fibrosis status is also used to determine appropriate HCV treatment regimens. Fibrosis indicates the amount of collagen present in the liver. The severity of fibrosis correlates with an increased risk for liver failure and hepatocellular carcinoma. (Ray, 2015) Fibrosis is most commonly assessed using the Metavir fibrosis score, which is a 5-point scale ranging from F0 (no fibrosis) to F4 (compensated cirrhosis). (AASLD/IDSA, 2017)

All oral direct-acting antivirals carry a boxed warning regarding risk of hepatitis B virus reactivation in patients coinfected with hepatitis C virus (HCV) and hepatitis B virus (HBV). The labeling states to test all patients for evidence of current or prior HBV infection before initiating treatment for HCV.

### Pharmacology

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Pharmacology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral Direct-Acting Antivirals</strong></td>
<td></td>
</tr>
<tr>
<td>Daklinza (daclatasvir)</td>
<td>Daclatasvir is an inhibitor of HCV nonstructural protein 5A (NS5A) and inhibits both viral RNA replication and virion assembly.</td>
</tr>
<tr>
<td>Epclusa (sofosbuvir/ velpatasvir)</td>
<td>Velpatasvir is an HCV NS5A inhibitor and sofosbuvir is an NS5B polymerase inhibitor.</td>
</tr>
<tr>
<td>Harvoni (ledipasvir/ sofosbuvir)</td>
<td>Ledipasvir inhibits the HCV nonstructural protein 5A (NS5A). The NS5A protein acts at several different points in the HCV life cycle and is necessary for viral replication, although its exact role is not fully understood. Sofosbuvir is a nucleotide analog prodrg of a direct-acting antiviral polymerase inhibitor. Sofosbuvir must be metabolized to the active moiety, GS-461203. GS-461203 binds nonstructural protein (NS) 5B of RNA-dependent RNA polymerase, terminating viral replication.</td>
</tr>
<tr>
<td>Mavyret (glecaprevir/ pibrentasvir)</td>
<td>Glecaprevir is an HCV NS3/4A protease inhibitor and pibrentasvir is an HCV NS5A inhibitor.</td>
</tr>
<tr>
<td>Olysio (simeprevir)</td>
<td>Simeprevir is a direct-acting antiviral protease inhibitors. It binds nonstructural protein (NS) 3/4A of serine protease, preventing the virus from replicating within host cells.</td>
</tr>
<tr>
<td>Sovaldi (sofosbuvir)</td>
<td>Sofosbuvir is a nucleotide analog prodrg of a direct-acting antiviral polymerase inhibitor. Sofosbuvir must be metabolized to the active moiety, GS-461203. GS-461203 binds nonstructural protein (NS) 5B of RNA-dependent RNA polymerase, terminating viral replication.</td>
</tr>
<tr>
<td>Technivie (ombitasvir, paritaprevir, and ritonavir)</td>
<td>Ombitasvir, paritaprevir, ritonavir fixed dose combination tablet includes a hepatitis C virus NS5A inhibitor (ombitasvir), a hepatitis C virus NS3/4A protease inhibitor (paritaprevir), and a CYP3A inhibitor (ritonavir) that inhibits CYP3A mediated metabolism of paritaprevir, thereby providing increased plasma concentration of paritaprevir.</td>
</tr>
<tr>
<td>Brand Name</td>
<td>Pharmacology</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Viekira Pak / Viekira XR</strong></td>
<td>Ombitasvir, paritaprevir, ritonavir fixed dose combination tablet includes a hepatitis C virus NS5A inhibitor (ombitasvir), a hepatitis C virus NS3/4A protease inhibitor (paritaprevir), and a CYP3A inhibitor (ritonavir) that inhibits CYP3A mediated metabolism of paritaprevir, thereby providing increased plasma concentration of paritaprevir. Dasabuvir is a hepatitis C virus non-nucleoside NS5B palm polymerase inhibitor, which is supplied as separate tablets in the copackage.</td>
</tr>
<tr>
<td><strong>Vosevi</strong></td>
<td>Vosevi is a fixed-dose combination of sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor; velpatasvir, an HCV NS5A inhibitor; and voxilaprevir, an HCV NS3/4A protease inhibitor.</td>
</tr>
<tr>
<td><strong>Zepatier</strong></td>
<td>Elbasvir is an inhibitor of HCV NS5A and grazoprevir is an inhibitor of HCV NS3/4A protease.</td>
</tr>
</tbody>
</table>

**Interferon Therapy**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Pharmacology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intron A</strong> (interferon alfa-2b)</td>
<td>Interferon alfa is a family of proteins that possess antiviral, antitumor and immunomodulating effects. Generally, interferons exert their cellular activities by binding to specific membrane receptors on the cell surface.</td>
</tr>
<tr>
<td><strong>Pegasys</strong> (peginterferon alfa-2a)</td>
<td>In pegylated interferons, polyethylene glycol (PEG) is attached to interferon as a protein modifying agent to decrease renal clearance and extend duration of action. This allows for once-weekly administration.</td>
</tr>
<tr>
<td><strong>PegIntron</strong> (peginterferon alfa-2b)</td>
<td></td>
</tr>
</tbody>
</table>

**Guidelines**

**American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA)**

The AASLD / IDSA provides guidance regarding when to initiate antiviral therapy in patients with HCV infection. (AASLD/IDSA, 2017) The guidelines state that most patients with chronic HCV infection will benefit from therapy and should be treated. Treatment of chronic HCV is not routinely recommended in patients with a short life expectancy. Acute HCV infection is typically not treated, although treatment may be warranted in some patients based on other risk factors. For such patients, the guidelines recommend monitoring HCV RNA for at least 12 to 16 weeks after symptom onset, and beginning antiviral therapy after this time if the infection does not clear spontaneously. Use the same regimens recommended for chronic HCV infection when antiviral therapy is warranted for acute HCV infection. (AASLD/IDSA, 2017)

The goal of antiviral therapy is to prevent long-term complications of chronic HCV, such as end-stage liver disease, hepatocellular carcinoma, and death. (AALSD/IDSA, 2017; Ghany, 2009; Ghany, 2011) Because long-term outcomes are difficult to assess, surrogate virologic markers (e.g., HCV RNA concentrations, changes in HCV RNA from baseline) may be evaluated in clinical trials and help with guiding therapy. According to AASLD/IDSA, the best predictor of long-term response is sustained virologic response (SVR). Sustained virologic response is defined as negative HCV RNA status after the completion of therapy. The SVR may be evaluated at any time after completing therapy, although time points commonly evaluated are 12 weeks (SVR12) or 24 weeks (SVR24) after the end of therapy. (AALSD/IDSA, 2017; Ghany, 2009; Ghany, 2011)
The AASLD / IDSA guidelines provide “recommended” and “alternative” antiviral regimens for most chronic HCV patient populations. (AASLD/IDSA, 2017) Recommended regimens provide the best efficacy and less toxicity, with shorter treatment durations, and lower pill burden. Alternative regimens have disadvantages (e.g., less supporting evidence, higher pill burden, or less efficacy or more toxicity in certain patient groups) compared with the recommended regimens. In some patient-specific situations, an alternative regimen may be the treatment of choice. The guidelines rate the level of evidence for each recommendation as Class I (evidence and/or general agreement that the treatment is effective), Class II, (conflicting evidence or differing opinion on efficacy), Class IIa (evidence or opinion are in favor of efficacy), Class IIb (efficacy is less well-established), or Class III (evidence or general agreement that treatment is not useful and effective and in some cases may be harmful); and the strength of each recommendation as Level A (data available from randomized controlled clinical trials or meta-analyses), Level B (data from a single randomized trial or nonrandomized trials), or Level C (data from cases studies, expert consensus, or standard of care). (AASLD/IDSA, 2017) The guidelines recommend specific antiviral regimens based on HCV genotype, presence or absence of cirrhosis, previous HCV therapies, and, for some regimens, presence or absence of certain RASs. Additional guidance is provided for special populations, including patients with HCV / HIV coinfection and renal impairment. The guidelines emphasize considering patient-specific factors such as drug-drug interactions, renal function, and liver function, when choosing a treatment regimen. (AASLD/IDSA, 2017)

• **AASLD/IDSA Recommendations for Initial Treatment**
  Elbasvir/grazoprevir (Zepatier), glecaprevir/pibrentasvir (Mavyret), ledipasvir/sofosbuvir (Harvoni), and sofosbuvir/velpatasvir (Epclusa) are recommended regimens for HCV genotype 1. Alternative regimens may include paritaprevir/ritonavir/ombitasvir/dasabuvir (Viekira Pak/ER) with or without ribavirin, simeprevir (Olysio) in combination with sofosbuvir (Sovaldi), and daclatasvir (Daklinza) in combination with sofosbuvir (Sovaldi). There are differences in recommendations based on presence or absence of compensated cirrhosis, genotype subtype (1a vs. 1b), or presence or absence of NSSA resistance-associated substitutions (RASs). For HCV genotype 2 and 3, Epclusa and Mavyret are recommended and Daklinza + Sovaldi is an alternative regimen. Sofosbuvir/velpatasvir/voxilaprevir is an alternative regimen for HCV genotype 3 with compensated cirrhosis when Y93H is present. For genotype 4, Harvoni, Mavyret, Epclusa, and Zepatier are recommended regimens and Technivie + ribavirin is an alternative. For genotypes 5 and 6, Epclusa, Harvoni, and Mavyret are all recommended regimens. (AASLD/IDSA, 2017)

• **AASLD/IDSA Recommendations for Retreatment**
  Recommendations for treatment-experienced individuals are given based on genotype (and subtype for genotype 1), presence or absence of compensated cirrhosis, prior failed regimen, and presence or absence of baseline NS5A RASs. (AASLD/IDSA, 2017)

  **Peginterferon/Ribavirin-Experienced**
  For HCV genotype 1, previously treated with pegylated interferon and ribavirin without cirrhosis, Epclusa, Harvoni, Mavyret, and Zepatier are recommended regimens and Viekira Pak/ER in combination with ribavirin, Olysio + Sovaldi, and Daklinza + Sovaldi are alternative regimens. For HCV genotype 1 with compensated cirrhosis, Epclusa, Mavyret, and Zepatier are recommended and Harvoni in combination with ribavirin for 12 weeks, Zepatier, and Viekira Pak/ER listed as alternative regimens. For HCV genotype 2, Epclusa and Mavyret are recommended and Daklinza + Sovaldi is an alternative regimen. For HCV genotype 3 without cirrhosis, Epclusa is the recommended regimen and alternative regimens include Daklinza + Sovaldi, Mavyret, and Vosevi (when Y93H is present). For HCV genotype 3 with compensated cirrhosis, Zepatier in combination with Sovaldi and sofosbuvir/velpatasvir/voxilaprevir are recommended regimens and Epclusa in combination with ribavirin and Mavyret are listed as alternative. For HCV genotype 4, Epclusa, Harvoni (for non-cirrhotics), Mavyret, and Zepatier are recommended regimens and Harvoni with ribavirin (for compensated cirrhosis), Technivie with ribavirin, and Zepatier are alternative regimens. For HCV genotype 5 and 6, Epclusa, Harvoni, and Mavyret are recommended. (AASLD/IDSA, 2017)

  **NS3 Protease Inhibitor-Experienced**
  For HCV genotype 1, previously treated with a protease inhibitor (telaprevir, boceprevir, or simeprevir) with peginterferon/ribavirin, Epclusa, Harvoni (for non-cirrhotics), and Mavyret are recommended, and Harvoni with ribavirin (for compensated cirrhotics and Zepatier are alternatives. (AASLD/IDSA, 2017)

  **Direct-Acting Antiviral-Experienced**
HCV Genotype 1: For individuals treatment-experienced with a sofosbuvir-containing regimen (no NS5A inhibitor), Mavyret, Vosevi (for genotype 1a), and Epclusa (for genotype 1b) are recommended, and Harvoni in combination with ribavirin for 12 weeks is an alternative regimen for non-cirrhotics (except when prior simeprevir failure). For NS5A inhibitor-experienced, Vosevi is recommended and Mavyret is an alternative regimen (except for those previously-treated with an NS3/4 protease inhibitor. (AASLD/IDSA, 2017)

HCV Genotype 2: For individuals previously treated with sofosbuvir and ribavirin, Epclusa and Mavyret are recommended. (AASLD/IDSA, 2017)

HCV Genotype 3: For individuals previously treated with direct-acting antivirals (including NS5A inhibitors), Vosevi is recommended and for those with cirrhosis, addition of ribavirin is recommended. (AASLD/IDSA, 2017)

HCV Genotype 4, 5, and 6: For individuals previously treated with direct-acting antivirals (including NS5A inhibitors), Vosevi is recommended. (AASLD/IDSA, 2017)

• **AASLD/IDSA Recommendations for Unique Populations**
  The guidance includes recommended and alternative regimens for HIV/HCV co-infection, decompensated cirrhosis, recurrent HCV post-liver transplant, patients with renal impairment, kidney transplant patients, management of acute HCV, HCV in pregnancy, and HCV in children.

**European Association for the Study of the Liver (EASL)**
EASL updated their recommendations on treatment of hepatitis C in September 2016. The guidelines identify the following available interferon-free treatment regimens as options for each of the HCV genotypes:

- For genotype 1: Sofosbuvir/ledipasvir with or without ribavirin; Sofosbuvir/velpatasvir with or without ribavirin; ombitasvir/paritaprevir/ritonavir with or without ribavirin; grazoprevir/elbasvir with or without ribavirin; and sofosbuvir + daclatasvir with or without ribavirin. The regimen of sofosbuvir + simeprevir with or without ribavirin is deemed suboptimal.
- For genotype 2 or 3: Sofosbuvir/velpatasvir with or without ribavirin and sofosbuvir + daclatasvir with or without ribavirin. Sofosbuvir with ribavirin is listed as suboptimal.
- For genotype 4: Sofosbuvir/ledipasvir with or without ribavirin; sofosbuvir/velpatasvir with or without ribavirin; ombitasvir/paritaprevir/ritonavir with or without ribavirin; grazoprevir/elbasvir with or without ribavirin; sofosbuvir/daclatasvir with or without ribavirin; and sofosbuvir + simeprevir with or without ribavirin. The guideline notes the recommendation for sofosbuvir/daclatasvir regimen in genotype 4 is based on limited clinical trial data, in vitro data, and extrapolation from results in genotype 1.
- For genotype 5 or 6: Sofosbuvir/ledipasvir with or without ribavirin; sofosbuvir/velpatasvir with or without ribavirin; and sofosbuvir + daclatasvir with or without ribavirin. There is no clinical trial data to support the recommendation of sofosbuvir + daclatasvir (recommendation based on in vitro data). (EASL, 2016)

**North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN)**
The NASPGAN notes that hepatitis C in children may be followed without treatment until adulthood due to the slow progression to fibrosis and the rarity of severe disease. Treatment should be considered for children who demonstrate persistently elevated serum aminotransferases or those with progressive disease (i.e., fibrosis on liver histology). NASPGAN also notes the counter-argument that treatment could be considered in children with mild disease given the potential for viral eradication and lack of predictors of progression. NASPGHAN refers to the AASLD recommendations for treatment using the FDA-approved combination of pegylated interferon and ribavirin for children ages 3-17 years. The recommended length of therapy is 48 weeks for genotypes 1 and 4 and 24 weeks for genotypes 2 and 3 in children. (Mack, 2012)

**Clinical Efficacy**

- **Daclatasvir (Daklinza)**
The ALLY-3 trial evaluated daclatasvir in combination with sofosbuvir for 12 weeks in 152 individuals with HCV genotype 3 infection. The trial included 101 treatment-naïve patients and 51 treatment-experienced patients. The majority of treatment-experienced patients had failed prior interferon-containing regimens and only 7 patients received prior sofosbuvir-containing regimens. Overall the SVR12 rate was 89% with an SVR12 of 90% in treatment-naïve patients and 86% in treatment-experienced individuals. Patients with cirrhosis had a reduced SVR12 rate of 58% (11 of 19 patients) in treatment-naïve and 69% (9 of 13 patients) in treatment-experienced compared to non-cirrhotics (SVR12 of 97% in treatment-naïve and 94% in treatment-experienced). (Nelson, 2015)
• Elbasvir/grazoprevir (Zepatier)

Four published trials evaluated rates of sustained virologic response at post-treatment week 12 (SVR12) with 12 weeks of elbasvir / grazoprevir in HCV GT-1 and GT-4. (Forns, 2015; Rockstroh, 2015; Roth, 2015; Zeuzem, 2015) The overall SVR12 rate was similar in treatment-naïve patients (96.3%), patients previously treated with a protease inhibitor plus RBV / pegIFN (96% with concomitant RBV), patients with end-stage renal disease (94%), and patients coinfected with HIV (94%). No published trials evaluated 16 weeks of elbasvir / grazoprevir plus RBV. This regimen is recommended for patients with GT-1a and NS5A RAVs and previously-treated GT-4 patients based on unpublished data.

• Glecaprevir/pibrentasvir (Mavyret)

Glecaprevir/pibrentasvir for 8-16 weeks has been studied in HCV genotypes 1-6 without cirrhosis who are treatment-naïve or treatment-experienced with pegylated interferon and ribavirin with or without sofosbuvir (ENDURANCE-1, 3, and 4 and SURVEYOR-1 and 2). SVR12 was 99% for genotype 1 (8 week regimen), 98% for genotype 2 (8 week regimen), 93% for genotype 4 (8 week regimen), and 100% for both genotype 5 and 6 (8 week regimen). Genotype 3 patients were included in the ENDURANCE-3 trial which evaluated glecaprevir/pibrentasvir for 8 weeks (non-randomized arm) or 12 weeks and daclatasvir in combination with sofosbuvir for 12 weeks. SVR12 was 94.9% for 8 weeks and 95.3% for 12 weeks of glecaprevir/pibrentasvir and 96.5% for daclatasvir with sofosbuvir. (AbbVie Inc., 2017)

Individuals with HCV genotypes 1, 2, 4, 5, or 6 with compensated cirrhosis who are treatment-naïve or treatment-experienced with pegylated interferon and ribavirin with or without sofosbuvir were enrolled in EXPEDITION-1 and received glecaprevir/pibrentasvir for 12 weeks. Overall the SVR12 was 99% (145/146). (AbbVie Inc., 2017) SURVEYOR-2 included individuals with HCV genotype 3 and evaluated 12 weeks of glecaprevir/pibrentasvir in treatment-naïve with compensated cirrhosis and 16 weeks for treatment-experienced with pegylated interferon/ribavirin with or without sofosbuvir (PRS), without cirrhosis or with compensated cirrhosis. The SVR12 rate in the treatment-naïve group (12 weeks) was 98% and 96% for PRS treatment experienced (16 weeks). (AbbVie Inc., 2017)

The EXPEDITION-4 trial included patients with severe renal impairment (chronic kidney disease stages 4 and 5) without cirrhosis or with compensated cirrhosis with HCV genotypes 1-6. Treatment-naïve or treatment-experienced with PRS patients were included. The overall SVR12 rate was 98%. (AbbVie Inc., 2017)

Patients with HCV genotype 1 who were NS5A inhibitor or NS3/4A protease inhibitor experienced were included in the MAGELLAN-1 trial. NS5A inhibitor experienced received glecaprevir/pibrentasvir for 16 weeks and the SVR12 for those protease-inhibitor naïve was 94% (16/17). For protease-inhibitor experienced individuals, glecaprevir/pibrentasvir was given for 12 weeks and the SVR12 for those who were NS5A inhibitor- naïve was 92% (23/25). Mavyret is not labeled for those both NS3/4A protease inhibitor and NSSA inhibitor-experienced due to higher rates of virologic failure and treatment-emergent drug resistance. (AbbVie Inc., 2017)

Mavyret is contraindicated in patients with severe hepatic impairment (Child-Pugh C) and not recommended in patients with moderate hepatic impairment (Child-Pugh B).

• Ledipasvir/sofosbuvir (Harvoni)

Ledipasvir/sofosbuvir dual therapy has been compared with ledipasvir/sofosbuvir plus ribavirin for the treatment of HCV genotype 1 infection. In treatment naïve patients, sustained virologic response at 12 weeks post-therapy (SVR12) occurred in at least 93% with ledipasvir/sofosbuvir, regardless of treatment duration (8, 12, or 24 weeks), ribavirin use, or cirrhosis status. In patients with relapse or nonresponse after peginterferon/ribavirin (± HCV protease inhibitor), the SVR12 rate was at least 94% with ledipasvir / sofosbuvir, regardless of treatment duration (12 or 24 weeks), or ribavirin use. In previously treated patients with cirrhosis, the SVR12 rate was numerically higher after a longer treatment duration (12 weeks: 19/22, 86%; 24 weeks: 22/22, 100%). (Afdhal, 2014a; Afdhal, 2014b; Kowdley, 2014) The SIRIUS trial enrolled 155 patients with HCV genotype 1 infection, compensated cirrhosis, and treatment-experienced (prior regimen of pegylated interferon and ribavirin followed by pegylated interferon, ribavirin, and an HCV protease inhibitor). The SVR12 rate for the ledipasvir/sofosbuvir with ribavirin for 12 weeks group was 96% compared to 97% for ledipasvir/sofosbuvir for 24 weeks. (Bourlière, 2015)

The ION-4 trial evaluated ledipasvir/sofosbuvir given for 12 weeks in treatment-naïve and treatment-experienced, non-cirrhotic patients with genotypes 1 and 4 infection with HIV-1 coinfection. All 8 patients with
genotype 4 HCV infection achieved SVR12. (Naggie, 2015) The unpublished Study 1119 trial evaluated treatment-naïve or treatment-experienced patients with genotype 4 or 5 HCV infection. Twelve (12) weeks of Harvoni resulted in an SVR12 rate of 93% for the 44 genotype 4 patients and 93% for the 41 genotype 5 patients. (Gilead Sciences, 2017) Efficacy for ledipasvir/sofosbuvir for genotype 6 HCV infection was demonstrated in an open-label, phase 2 trial. Ledipasvir/sofosbuvir was given for 12 weeks to 25 treatment-naïve or treatment-experienced patients and 24 patients (96%) achieved SVR12. (Gane, 2015)

Ledipasvir/sofosbuvir has not been compared with other combination regimens using recommended oral HCV antivirals (e.g., simeprevir, sofosbuvir). Retreatment with ledipasvir/sofosbuvir or treating individuals who have failed ombitasvir/paritaprevir/ritonavir and dasabuvir combination therapy with ledipasvir/sofosbuvir has not been evaluated.

- **Ombitasvir/Paritaprevir/Ritonavir (Technivie)**

  The PEARL-I trial enrolled 135 patients with genotype 4 HCV infection without cirrhosis. Treatment-naïve patients (n = 86) received ombitasvir/paritaprevir/ritonavir (OBV/PTV/r) with or without ribavirin for 12 weeks. Patients previously treated with pegylated interferon and ribavirin (n = 49) received OBV/PTV/r without ribavirin for 12 weeks. The SVR12 rate was 100% for treatment-naïve and treatment-experienced patients who received OBV/PTV/r with ribavirin. The SVR12 rate was 91% for treatment-naïve patients who received OBV/PTV/r without ribavirin. (Hézode, 2015)

  The AGATE-I and AGATE-II open-label trials enrolled adults with genotype 4 HCV infection who were treatment-naïve or treatment-experienced with interferon-based regimens. AGATE-I was multinational and included individuals with compensated cirrhosis and AGATE-II included individuals with and without compensated cirrhosis from multiple sites in Egypt. AGATE-I treatment regimen was ombitasvir/paritaprevir/ritonavir with ribavirin for 12 weeks or 16 weeks and resulted in an SVR12 rate of 97% (57/59) and 98% (60/61), respectively. (Asselah, 2016) AGATE-II demonstrated an SVR12 rate of 97% (30/31) for individuals with cirrhosis treated with ombitasvir/paritaprevir/ritonavir with ribavirin for 12 weeks and an SVR12 of 93% (27/29) for individuals with cirrhosis treated with the same regimen for 24 weeks. (Waked, 2016)

  In October 2015, the U.S. Food and Drug Administration (FDA) issued a warning that Technivie can cause serious liver injury mostly in patients with underlying advanced liver disease. (US FDA, 2015) Technivie is only indicated in HCV genotype 4 infection without cirrhosis. Technivie is contraindicated in patients with moderate to severe hepatic impairment and carries a warning and precaution regarding hepatic decompensation and hepatic failure in patients with cirrhosis. (Abbvie Inc., 2015a)

- **Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir (Viekira Pak, Viekira XR)**

  Ombitasvir/paritaprevir/ritonavir and dasabuvir combination therapy (Viekira Pak) has been studied in individuals with HCV genotype 1 infection. SAPPHIRE-I enrolled treatment-naïve and SAPPHIRE-II enrolled treatment-experienced individuals (failed prior therapy with pegylated interferon and ribavirin) with genotype 1a and 1b HCV infections without cirrhosis. Subjects were treated with Viekira Pak plus ribavirin for 12 weeks. The SVR12 rate in both trials was 96%. (Feld, 2014; Zeuzem, 2014) PEARL II and III examined the effect of adding ribavirin to Viekira Pak for genotype 1b individuals without cirrhosis. PEARL II included patients who had failed prior therapy with pegylated interferon and ribavirin and PEARL III included those who were treatment-naïve. SVR12 rates of 97-100% were demonstrated. (Andreone, 2014; Ferenci, 2014) PEARL IV also evaluated the effect of adding ribavirin to Viekira Pak for treatment-naïve, non-cirrhotic, genotype 1a patients. The SVR12 for Viekira Pak without ribavirin was 90% compared with 97% for the group receiving Viekira Pak with ribavirin. (Ferenci, 2014)

  Viekira Pak with ribavirin was evaluated in genotype 1a or 1b, treatment-naïve or treatment-experienced individuals with cirrhosis in the TURQUOISE-II trial. This study compared the treatment duration of 12 weeks versus 24 weeks and found SVR12 rates of 92% and 96%, respectively. (Poordad, 2014) Viekira Pak with ribavirin has also been studied in HIV/HCV co-infected individuals (TURQUOISE-I; Wyles, 2014; AbbVie Inc, 2014) and in the post-liver transplant population without evidence of advanced fibrosis (CORAL-I; Kwo, 2014).

  Viekira Pak has not been compared with other combination regimens using HCV oral direct-acting antiviral agents (e.g., boceprevir, ledipasvir, ledipasvir/sofosbuvir, simeprevir, sofosbuvir, telaprevir). Viekira Pak has not been evaluated in individuals treatment-experienced with any HCV oral direct-acting antiviral agent.
In October 2015, the U.S. Food and Drug Administration (FDA) issued a warning that Viekira Pak can cause serious liver injury mostly in patients with underlying advanced liver disease. (US FDA, 2015) Viekira Pak is contraindicated in patients with moderate to severe hepatic impairment and carries a warning and precaution regarding hepatic decompensation and hepatic failure in patients with cirrhosis. (Abbvie Inc., 2015b)

Viekira XR received FDA approval based on clinical studies using Viekira Pak and 2 bioavailability studies conducted comparing Viekira Pak and Viekira XR.

- **Sofosbuvir (Sovaldi)**
  Sofosbuvir / ribavirin ± peginterferon has been compared with ribavirin / peginterferon for treating HCV infection. Sofosbuvir / ribavirin for 12 weeks was noninferior to ribavirin / peginterferon for 48 weeks in treatment naive patients with HCV genotype 2 or 3. (Lawitz, 2013) In treatment naïve patients given sofosbuvir/ribavirin/ peginterferon for 12 weeks, sustained virologic response at 12 weeks post-therapy (SVR12) occurs in 89% of genotype 1 patients, 96% of genotype 4 patients, and 77% patients with genotypes 5 or 6. (Lawitz, 2013) In the VALENCE trial, the SVR12 rate with sofosbuvir/ribavirin is 97% in genotype 2 treatment-naive patients treated for 12 weeks; and 93% in genotype 3 treatment-naive patients treated for 24 weeks. In patients with relapse or nonresponse to prior interferon-based therapy, the rate of SVR12 with sofosbuvir/ribavirin is 90% in genotype 2 patients treated for 12 weeks, and 77% in genotype 3 patients treated for 24 weeks. (Gilead Sciences, Inc., 2013) Response rates with sofosbuvir/ribavirin are similar in patients with HCV/HIV coinfection, and vary by HCV genotype and prior treatment status. Overall, response rates with sofosbuvir regimens are lower in genotype 3 than other genotypes, and in patients with cirrhosis than in patients without cirrhosis. Sofosbuvir regimens have not been directly compared with regimens using other HCV antivirals (e.g., boceprevir, simeprevir, telaprevir).

- **Sofosbuvir/velpatasvir (Epclusa)**
  Sofosbuvir/velpatasvir has been evaluated in genotypes 1-6, including those with compensated and decompensated cirrhosis. There is no data evaluating the regimen in recurrent HCV post-liver transplant or in severe renal impairment/end stage renal disease. The ASTRAL-1 trial enrolled patients with genotype 1, 2, 4, 5, or 6 HCV infection, with or without compensated cirrhosis, and treatment-naïve or treatment-experienced (excluded prior use of any nucleotide HCV NS5B inhibitor or any NS5A inhibitor). Treatment was sofosbuvir/velpatasvir for 12 weeks or placebo (deferred treatment) and the overall SVR12 rate was 99%. (Feld, 2015) The ASTRAL-2 trial enrolled individuals with genotype 2 infection, with or without compensated cirrhosis, and treatment-naïve or treatment-experienced (excluded prior use of any nucleotide HCV NS5B inhibitor or any NS5A inhibitor). Treatment was sofosbuvir/velpatasvir for 12 weeks or sofosbuvir and ribavirin for 12 weeks. The SVR12 rate with sofosbuvir/velpatasvir was 99% and was superior to the SVR12 rate of sofosbuvir and ribavirin of 94% (p = 0.02). (Foster, 2015) The ASTRAL-3 trial enrolled individuals with genotype 3 infection, with or without compensated cirrhosis, and treatment-naïve or treatment-experienced (excluded prior use of any nucleotide HCV NS5B inhibitor or any NS5A inhibitor). Treatment was sofosbuvir/velpatasvir for 12 weeks resulted in a superior SVR12 rate of 95% compared to 80% with sofosbuvir and ribavirin for 24 weeks (p < 0.001). (Foster, 2015)

  The ASTRAL-4 trial enrolled 267 treatment-naïve or treatment-experienced individuals with HCV genotype 1 through 6 and decompensated cirrhosis (Child-Pugh-Turcotte class B at screening). Patients were randomized to receive sofosbuvir/velpatasvir for 12 weeks, sofosbuvir/velpatasvir with ribavirin for 12 weeks, or sofosbuvir/velpatasvir for 24 weeks. The majority of patients had HCV genotype 1 infection (78%). The overall SVR12 rate was 83% for the group receiving sofosbuvir/velpatasvir for 12 weeks; 94% for those receiving sofosbuvir/velpatasvir with ribavirin for 12 weeks; and 86% for those receiving sofosbuvir/velpatasvir for 24 weeks. (Curry, 2015)

- **Sofosbuvir/velpatasvir/voxilaprevir (Vosevi)**
  Vosevi was evaluated in 2 randomized, controlled, phase 3 trials enrolling direct-acting antiviral (DAA)-experienced patients with HCV genotypes 1-6 (POLARS-1 and POLARIS-4). Vosevi was also evaluated in 2 trials (POLARIS-2 and POLARIS-3) enrolling treatment-naïve patients. (Jacobson, 2017) Vosevi is not FDA approved for treatment-naïve patients.

  POLARIS-1 randomized patients with HCV genotype 1-6 who had been previously treated with an NS5A inhibitor to sofosbuvir/velpatasvir/voxilaprevir once daily for 12 weeks (n = 263) or placebo (n = 152). Vosevi-
treated patients had an overall SVR of 96% (253/263) with 6 patients relapsing, 1 with on-treatment failure, 2 withdrawing consent, and 1 lost to follow-up. (Bourlière, 2017)

POLARIS-4 randomized patients previously treated with DAA-therapy other than NS5A inhibitors with HCV genotype 1, 2, or 3. Patients received either Vosevi once daily for 12 weeks (n = 182) or Epclusa once daily for 12 weeks (n = 151). Overall, the SVR12 with Vosevi was 98% and with Epclusa was 90%. SVR12 rates by genotype were as follows: 1a – Vosevi = 98% and Epclusa = 89%; 1b – Vosevi = 96% and Epclusa = 95%; 2 – Vosevi = 100% and Epclusa = 97%; 3 – Vosevi = 96% and Epclusa = 85%. (Bourlière, 2017)

- **Combination Therapy of Simeprevir (Olysio) and Sofosbuvir (Sovaldi)**

  COSMOS was a randomized, controlled, open-label, phase 2 trial of patients with HCV genotype 1 that evaluated the efficacy of simeprevir 150 mg/day plus sofosbuvir 400 mg/day with or without weight-based ribavirin. Patients were enrolled and randomized in 2 separate cohorts: Cohort 1 included 80 patients with prior nonresponse to ribavirin / peginterferon, and with METAVIR score of F0 to F2; and Cohort 2 included 87 patients who were treatment naïve or with prior nonresponse to ribavirin/peginterferon and with METAVIR score of F3 to F4. Within each cohort, patients were randomized to simeprevir/sofosbuvir for 12 weeks, simeprevir/sofosbuvir/ribavirin for 12 weeks, or simeprevir/sofosbuvir/ribavirin for 24 weeks. In Cohort 1, sustained virologic response 12 weeks after completing therapy (SVR12) was achieved in 90% of patients and the SVR12 in Cohort 2 was achieved in 94% of patients. Use of ribavirin, duration of treatment, or use of previous treatment did not significantly affect the outcome. There was no on-treatment virological failure. At the conclusion of treatment, 6 patients experienced viral relapse. Only 2% (n = 4) patients discontinued treatment due to adverse events. (Lawitz, 2014) The product labeling for Olysio provides the SVR12 for patients with METAVIR fibrosis score of F4 (i.e., cirrhotic). The 12-week regimen of simeprevir and sofosbuvir produced an SVR12 of 86% (6/7) and the 24-week regimen yielded an SVR12 of 100% (10/10). (Janssen Therapeutics, 2015)

The phase 3 OPTIMIST-1 trial is unpublished and evaluated 8 and 12 weeks of simeprevir with sofosbuvir in treatment-naïve and treatment-experienced patients with HCV genotype 1 infection and no cirrhosis. (Kwo, 2015) The OPTIMIST-2 trial enrolled 103 treatment-naïve and treatment-experienced patients with HCV genotype 1 infection and cirrhosis. The SVR12 rate achieved with simeprevir and sofosbuvir for 12 weeks was 83%. (Lawitz, 2015)

**Not Covered Uses**

- **Simeprevir (Olysio) in combination with pegylated interferon and ribavirin**

  Simeprevir/ribavirin/peginterferon have been compared with ribavirin/peginterferon for treating HCV genotype 1 infection. In treatment naïve patients or patients with relapse after interferon-based therapy, the rate of sustained virologic response (SVR) at 12 weeks post-therapy is up to 80% with the labeled simeprevir regimen (simeprevir/ribavirin/peginterferon for 12 weeks, followed by ribavirin/peginterferon for 12 or 36 weeks using response guided therapy) and 37% to 50% with ribavirin/peginterferon for 48 weeks. (Janssen Therapeutics, 2013) In patients with prior relapse or prior poor response after ribavirin/peginterferon, the rate of SVR at 24 weeks post-therapy is 67% with the labeled simeprevir regimen (simeprevir/ribavirin/peginterferon for 12 weeks, followed by ribavirin/peginterferon for 36 weeks) and 23% with ribavirin/peginterferon for 48 weeks. (Zeuzem, 2014) The presence of genotype 1a with the Q80K mutation decreases likelihood of response to simeprevir in treatment naïve patients and patients with prior interferon relapse. The AASLD/IDSA guidance no longer recommends the use of simeprevir with pegylated interferon and ribavirin for initial treatment or retreatment of HCV genotype 1 infection. (AASLD/IDSA/IAS-USA, 2017)

### Appendix 1

**Fibrosis Scoring Systems**

(AASLD Practice Guidelines; Ghany, 2009)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Metavir</th>
<th>Batts-Ludwig</th>
<th>IASL</th>
<th>Ishak</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No fibrosis</td>
<td>No fibrosis</td>
<td>No fibrosis</td>
<td>No fibrosis</td>
</tr>
<tr>
<td>1</td>
<td>Periportal fibrotic expansion</td>
<td>Fibrous portal expansion</td>
<td>Mild fibrosis</td>
<td>Fibrous expansion of some portal areas, with or</td>
</tr>
<tr>
<td>Stage</td>
<td>Metavir</td>
<td>Batts-Ludwig</td>
<td>IASL</td>
<td>Ishak</td>
</tr>
<tr>
<td>-------</td>
<td>--------------------------</td>
<td>-----------------------</td>
<td>-----------------------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>2</td>
<td>Periportal septae  1 (septum)</td>
<td>Rare bridges or septae</td>
<td>Moderate fibrosis</td>
<td>Fibrous expansion of most portal areas with or without short fibrous septa</td>
</tr>
<tr>
<td>3</td>
<td>Porto-central septae</td>
<td>Numerous bridges or septae</td>
<td>Severe fibrosis</td>
<td>Fibrous expansion of most portal areas with occasional portal to portal bridging</td>
</tr>
<tr>
<td>4</td>
<td>Cirrhosis</td>
<td>Cirrhosis</td>
<td>Cirrhosis</td>
<td>Fibrous expansion of most portal areas with marked bridging (portal to portal and portal to central)</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td>Marked bridging (portal to portal and portal to central) with occasional nodules (incomplete cirrhosis)</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td>Cirrhosis</td>
</tr>
</tbody>
</table>

IASL = International Association for the Study of the Liver

### Appendix 2

#### Child-Turcotte-Pugh Classification

The Child-Turcotte-Pugh or Child-Pugh score is an FDA-recommended classification for assessing hepatic impairment. It is a classification of severity of cirrhosis with five different parameters assigned scores of 1 to 3, with 3 being the most negative or severe finding, that are then added together. The parameters are hepatic encephalopathy, ascites, total bilirubin, serum albumin, and prothrombin time.

**Child-Pugh Score Uses Five Clinical Measures of Hepatic Impairment**

*Each Is Scored on a Scale of 1 to 3 (3 = highest severity)*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Points Assigned</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Ascites</td>
<td>Absent</td>
</tr>
<tr>
<td>Bilirubin, total (mg/dL)</td>
<td>1.0 - 2.0</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt; 3.5</td>
</tr>
<tr>
<td>Prothrombin Time:</td>
<td></td>
</tr>
<tr>
<td>° Seconds Prolonged</td>
<td>1.0 – 4.0</td>
</tr>
<tr>
<td>° International Normalized Ratio (INR)</td>
<td>&lt; 1.7</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
</tr>
</tbody>
</table>

Encephalopathy is classified as Grade 0 to 4 as follows:

- 0 — No abnormality detected
- 1 — Shortened attention span, impaired addition and subtraction skills, mild euphoria or anxiety
- 2 — Lethargy, apathy, disoriented to time, personality change, inappropriate behavior
- 3 — Somnolence, semi-stupor, responsive to stimuli, confused when awake, gross disorientation
- 4 — Coma, little or no response to stimuli, mental state not testable
The Grade of Hepatic Impairment Is Equal to the Child-Pugh Score/Classification of A, B, or C

- Once each measure is scored, points are totaled to classify the degree of hepatic impairment
- Degree of hepatic impairment is classified by one of three Grades - A, B, or C as follows:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Mild; well compensated disease</td>
<td>5 – 6</td>
</tr>
<tr>
<td>B</td>
<td>Moderate; significant functional compromise</td>
<td>7 – 9</td>
</tr>
<tr>
<td>C</td>
<td>Severe; decompensated disease</td>
<td>10 – 15</td>
</tr>
</tbody>
</table>

Coding/Billing Information

Note: Hepatitis C Therapy is typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. Medical drug coding and diagnosis codes, however, are generally not required for pharmacy claims submissions. Interferon therapy for hepatitis C requires medical drug coding and is listed as follows:

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Covered when medically necessary:

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J9214</td>
<td>Injection, interferon, alfa-2b, recombinant, 1 million units</td>
</tr>
<tr>
<td>S0145</td>
<td>Injection, pegylated interferon alfa-2a, 180 mcg per ml</td>
</tr>
<tr>
<td>S0148</td>
<td>Injection, pegylated interferon alfa-2b, 10 mcg</td>
</tr>
</tbody>
</table>

References


