Summary
The standard of care for treating chronic hepatitis C (CHC) is rapidly evolving. On March 21, 2014, the Infectious Diseases Society of America (IDSA) in collaboration with the American Association for the Study of Liver Diseases (AASLD) developed web-based, evidence-based, expert-derived recommendations for hepatitis C management. The guidance is a fluid document, updated as the treatment landscape evolves and new therapies are approved. This Issues Document is intended to describe current and future regimens and guidance for treating CHC and how Express Scripts and Accredo are prepared to manage the evolving market.

Take-Away Points
- The standard of care for treating chronic hepatitis C is rapidly evolving.
- Hepatitis C treatment guidance will continually be updated as new data and treatment options become available.
- Beginning in the second half of 2014, new all-oral regimens for genotype 1 CHC will compete in the market.
- For most patients, currently-available oral medications to treat genotype 1 CHC (the most common genotype in the US) require treatment with injectable peginterferon alfa.
- Many patients with genotype 1 CHC and prescribers are waiting for new all-oral options to begin treatment.
- Per member per year (PMPY) spend on hepatitis C medication is expected to increase significantly over the next few years.
- Express Scripts and Accredo have the tools and expertise to help manage hepatitis C.

Hepatitis C Market
Hepatitis C is an infectious disease of the liver caused by the hepatitis C virus (HCV). Past or current injection drug use is the most important risk factor for HCV infection. Chronic infection of HCV can cause serious complications including liver disease, cirrhosis (scarring of the liver), liver failure, and liver cancer. In the US, hepatitis C is the leading cause of liver transplantation and contributes to more than 10,000 deaths annually. There are approximately 3.2 million people in the US with CHC and most don’t know they have the condition. There are six major strains of the virus, called genotypes. Genotype 1 is the most common strain in the US, representing approximately 78% of cases. Genotype 1 can be broken down into two major subtypes, 1a and 1b. In the US, genotype 1a accounts for approximately 70% of genotype 1 infections and is typically more difficult to treat. Nearly half of all patients with genotype 1a CHC have the NS3 Q80K polymorphism rendering them ineligible for some therapies. Genotype 2 represents approximately 13% of cases, genotype 3 represents approximately 6% of cases and genotypes 4-6 represent approximately 3% of cases.

In May 2012, the Centers for Disease Control and Prevention (CDC) issued a recommendation that anyone born between 1945 and 1965 (baby boomers) should receive a one-time blood test to see if they are infected with HCV. In the U.S., baby boomers account for more than 75% of all patients with hepatitis C. The US Preventative Services Task Force (USPSTF) echoed this recommendation in June 2013. Many baby boomers may have been infected from contaminated blood or blood products before widespread screening of the blood supply began in 1992. Others may have become infected from prior injection drug use. Nearly half of people with HCV are unsure how or when they were exposed to the virus.

Hepatitis C Treatment
Until mid-2011, hepatitis C was treated with injectable peginterferon alfa (once weekly) and oral ribavirin (twice daily) for almost a year. Incivek® (telaprevir tablet – Vertex) and Victrelis® (boceprevir capsules – Merck), oral protease inhibitors, were approved by the US Food and Drug Administration (FDA) in May 2011 for patients with genotype 1 CHC. When added onto peginterferon alfa and ribavirin higher viral cure rates were achieved with these three-drug therapies. On November 22, 2013, Janssen’s Olysio™ (simeprevir capsules), another oral protease inhibitor, was approved for patients with genotype
1 CHC (who do not have the Q80K polymorphism) in combination with peginterferon alfa and ribavirin. On December 6, 2013, Gilead’s Sovaldi™ (sofosbuvir tablets), an oral nucleotide analog polymerase inhibitor, was approved for certain patients with genotypes 1-4 CHC. Sovaldi is given with peginterferon alfa and ribavirin for genotypes 1 and 4 CHC and as an all-oral regimen with ribavirin for genotypes 2 and 3 CHC. Additional all-oral (interferon-free) regimens for CHC are expected to reach the market in the second half of 2014.

The goal of treatment is eradication of the virus to prevent complications of liver disease. Viral cure is assessed as sustained viral response (SVR) meaning there is no detectable virus in the blood 12 weeks after finishing treatment. Prior to the approvals of Incivek and Victrelis, SVR rates for patients with genotype 1 CHC (in clinical trials) were approximately 50% compared to closer to 80% for other genotypes. Real-world SVR rates are typically much lower as patients may be non-adherent to therapy, typically due to adverse effects (AEs) from medication. Peginterferon alfa is generally not well-tolerated and can cause a variety of AEs including flu-like symptoms and depression. Ribavirin is also not well-tolerated and is often associated with hemolytic anemia. When Incivek or Victrelis were added onto peginterferon alfa and ribavirin in patients with genotype 1 CHC, SVR rates improve to approximately 70% and some patients only need treatment for 24 weeks, instead of 48 weeks when peginterferon alfa and ribavirin were used alone. A primary safety concern with Incivek is severe rash and both Incivek and Victrelis frequently cause anemia. Triple therapy with Incivek and Victrelis is no longer recommended in patients with genotype 1 CHC due to markedly inferior AE profiles, longer treatment duration, higher pill burden, drug-drug interactions, more frequent of dosing, intense monitoring for continuation and stopping of therapy, and the requirement for these agents to be taken with high-fat meals, relative to the preferred and alternative recommendations in the guidance.

When Olysio is added onto peginterferon alfa and ribavirin in patients with genotype 1 CHC, SVR rates improve to around 80%. The effectiveness of Olysio is greatly reduced in patients infected with the genotype 1a HCV with an NS3 Q80K polymorphism. Approximately 25% of all genotype 1 patients in the US have this polymorphism (50% of all patients with genotype 1a). Screening patients with genotype 1a infection for this polymorphism at baseline is strongly recommended, and if present a treatment other than Olysio should be used. Use of Olysio can be associated with photosensitivity and rash.

Sovaldi was approved to treat patients with genotypes 1-4, including those with hepatocellular carcinoma (HCC) awaiting liver transplantation and those with HCV/human immunodeficiency virus (HIV) co-infection. When Sovaldi is added onto ribavirin and/or peginterferon alfa (depending on genotype), SVR rates improve to around 90% (varies widely based on genotype/regimen). Sovaldi is generally well-tolerated. Use of Sovaldi can be associated with anemia; however, the incidence of anemia is much lower than what is seen with Incivek and Victrelis. Use of Sovaldi to treat genotypes 2 and 3 is the first all-oral (interferon-free) regimen to gain FDA approval.

The average wholesale price (AWP) for the four oral, direct-acting antiviral (DAA) medications that are currently available to treat genotype 1 CHC can be found in Table 1.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Supplied</th>
<th>Cost/Tab or Cap</th>
<th>Dose</th>
<th>Weekly Cost</th>
<th>Treatment Duration Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incivek</td>
<td>375mg tab</td>
<td>$157.51</td>
<td>1125mg BID</td>
<td>$6,615</td>
<td>$79,385 (12 weeks)</td>
</tr>
<tr>
<td>Victrelis</td>
<td>200mg cap</td>
<td>$21.73</td>
<td>800mg TID</td>
<td>$1,827</td>
<td>$43,848 (24 weeks)</td>
</tr>
<tr>
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<td></td>
<td>$58,468 (32 weeks)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$80,388 (44 weeks)</td>
</tr>
<tr>
<td>Olysio</td>
<td>150mg cap</td>
<td>$948</td>
<td>150mg QD</td>
<td>$6,636</td>
<td>$79,632 (12 weeks)</td>
</tr>
<tr>
<td>Sovaldi</td>
<td>400mg tab</td>
<td>$1,200*</td>
<td>400mg QD</td>
<td>$8,400</td>
<td>$100,800 (12 weeks)†</td>
</tr>
</tbody>
</table>

*Wholesale Acquisition Cost (WAC) of Sovaldi is $1,000 per tablet.
†WAC of Sovaldi for 12 weeks is $84,000.
Pipeline Medications for Hepatitis C

There is significant development of pipeline all-oral regimens to treat CHC. Currently, physicians and patients are waiting for all-oral regimens to reach the market to initiate treatment. This phenomena is called patient “warehousing”. Once all-oral regimens are available to treat genotype 1 CHC, per member per year (PMPY) spend on hepatitis C is expected to increase significantly. These have been granted breakthrough therapy designations by FDA. A breakthrough therapy is a drug or regimen that is used to treat a serious or life-threatening condition and preliminary evidence indicates that the drug or regimen may demonstrate substantial improvement over existing therapies. FDA expedites the development and review of breakthrough therapies, thus it is likely that these treatments may reach the market prior to their expected action dates.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Mechanism of Action</th>
<th>Patient Genotype</th>
<th>FDA Action Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>ledipasvir / sofosbuvir</td>
<td>Gilead</td>
<td>NS5a inhibitor/nucleotide analog polymerase inhibitor</td>
<td>Genotype 1 CHC</td>
<td>10/10/2014</td>
</tr>
<tr>
<td>daclatasvir / asunaprevir</td>
<td>Bristol-Myers Squibb</td>
<td>NS5a inhibitor/protease inhibitor</td>
<td>Genotype 1b CHC</td>
<td>12/07/2014</td>
</tr>
<tr>
<td>ABT-450 /ritonavir/ ombitasvir/dasabuvir</td>
<td>AbbVie / Enanta</td>
<td>ritonavir-boosted protease inhibitor/NS5a inhibitor/ non-nucleoside polymerase inhibitor</td>
<td>Genotype 1 CHC</td>
<td>12/21/2014</td>
</tr>
<tr>
<td>MK-5172/MK-8742</td>
<td>Merck</td>
<td>protease inhibitor / NS5a inhibitor</td>
<td>Genotype 1 CHC</td>
<td>2H:2015</td>
</tr>
<tr>
<td>daclatasvir / asunaprevir / BMS-791325</td>
<td>Bristol-Myers Squibb</td>
<td>NS5a inhibitor/protease inhibitor/ non-nucleoside polymerase inhibitor</td>
<td>Genotype 1 CHC</td>
<td>2H:2015</td>
</tr>
</tbody>
</table>

Current AASLD/IDSA Guidance Highlights

On March 21, 2014 the AASLD/IDSA developed guidance for the management of hepatitis C. This guidance will be updated as new information becomes available and should be consulted for the most up-to-date information. The recommendations are based on evidence and reflect the best possible management for a given patient and a given point of disease progression. The level of evidence for each patient group varies, as does the strength of the recommendation, and is graded as such.

Sovaldi is prominently recommended as part of most regimens regardless of genotype or prior treatment history. Sovaldi is recommended according to its FDA approved uses as well as many off-label uses. In some patient populations the guidelines recommend combination of Sovaldi with Olysio with or without ribavirin. Most patients are eligible for 12 weeks of therapy, while certain populations still require 24-48 weeks. Dual therapy with peginterferon and ribavirin are no longer considered the standard of care for patients with genotypes 1-4 HCV. Triple therapy with Incivek and Victrelis is no longer recommended in patients with genotype 1 CHC.

Further guidance on the following topics is expected to be published this summer: when to treat, monitoring patients who are on or who have completed therapy, and management of acute HCV infection.
Express Scripts’ Response

Express Scripts and Accredo Specialty Pharmacy have the tools and expertise to help manage hepatitis C. Some of the available tools can be found below.

**Drug Choices**
Express Scripts has point-of-service utilization management strategies such as Prior Authorization, Preferred Specialty Management, Drug Quantity Management and Clinical Days’ Supply to determine appropriate coverage of these medications.

**Health Choices**
Express Scripts has retrospective utilization management strategies such as ExpressAlliance and RationalMed that are designed to improve adherence and enhance care for patients with chronic and complex conditions such as hepatitis C.

**Specialty Care Management Programs**
Accredo Therapeutic Resource Centers (TRCs) offer specialized clinical care to ensure patients get the specific drug and disease information they need to improve adherence and achieve the best possible outcome from their therapy. Through our care management approach at Accredo, specialized pharmacists and nurses work with patients who have hepatitis C every day. They verify a patient’s genotype before starting therapy to make sure patients are taking the right combination of medications for the appropriate amount of time. They also conduct outreach to collect viral level information where appropriate and make therapy duration recommendations. Our clinicians provide the patient with education about potential side effects, management suggestions to mitigate those side effects, and information and techniques to help optimize medication adherence.