International Health Briefs

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Advances in Hepatitis C Treatment

Dear Client,

The rapidly expanding family of new, highly effective drugs to treat hepatitis C is likely to lead to an explosion in insured costs for this condition. Per-patient costs of these treatments are already in the hundreds of thousands of dollars. As these treatments are still new, their high costs are unlikely to abate soon.

This brief explains hepatitis C, discusses the new drugs and their efficacy, and provides guidance around verification of medical necessity of treatment, claims considerations and underwriting considerations.

Best wishes,

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RGA

What is Hepatitis C?

Hepatitis C is a disease of the liver caused by the hepatitis C virus (HCV). This virus, which was first identified in 1989, is blood-borne (i.e., transmitted by virus-infected blood), and is unrelated to the other known hepatitis viruses (A, B, D and E).

Estimates place the number of people globally who are infected with HCV at approximately 130-170 million (or 2% to 3% of the world's population), and between 350,000 and 500,000 as the number who die annually from hepatitis C-related liver disease. Both the National Academy of Medicine (U.S.) and the National Institute of Allergy and Infectious Diseases (U.S.) have classified hepatitis C as an emerging infectious disease.

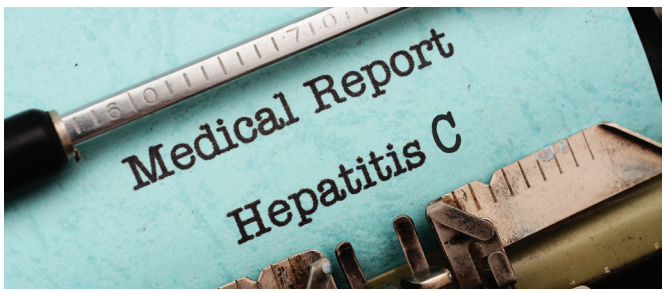
According to estimates, HCV infection prevalence in Western Europe and North America is approximately 1% to 2% of the population, approximately 3% to 4% in parts of the Mediterranean and Asia, and significantly higher in parts of central Africa and Egypt, with some estimates placing prevalence as high as 17.5%. In the U.S., HCV now accounts for more deaths than HIV.

Transmission: HCV is most commonly transmitted through the shared use of injecting equipment, including tattoo needles. In some countries, transmission has been associated with inadequate sterilisation of medical equipment in health care settings.

HCV can also be transmitted via transfusions of unscreened blood and blood products, although this has reduced considerably. Sexual and mother-to-child transmission can occur as well, but incidence of these is low.

Symptoms and Progression: Progression of hepatitis C is not uniform. It can resolve without treatment, result in a mild short-term illness, or can cause a serious and potentially life-limiting long-term (chronic) condition.

The incubation period for HCV is between two weeks and six months. Approximately 15% to 20% of these infections clear spontaneously (without treatment) within six months. The rest of the cases either clear with treatment within six months (commonly referred to as 'acute' hepatitis C) or need further treatment, at which point the HCV infection is considered to have become chronic. Approximately 15%



to 30% of individuals with chronic hepatitis C will develop cirrhosis of the liver, and a small percentage of those with cirrhosis will also develop liver cancer.

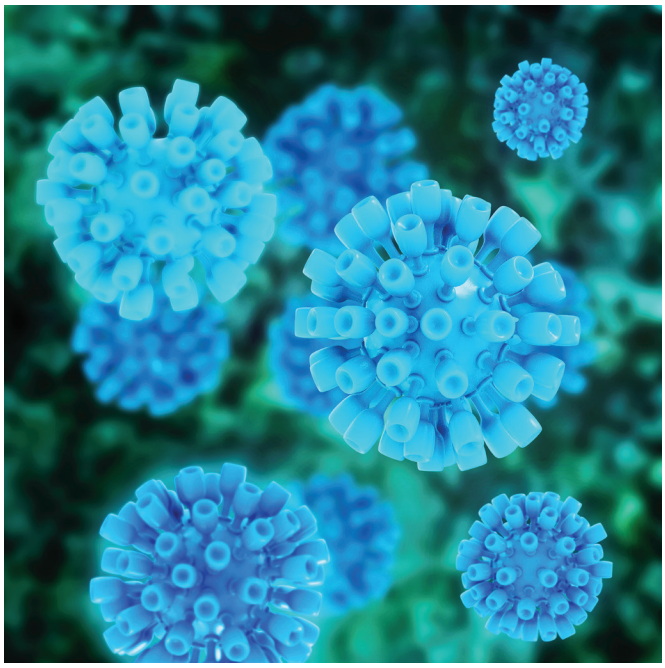
Hepatitis C's early stages are often asymptomatic. Symptoms, if they do develop, occur within a few weeks of infection, are generally flulike and can include fever, decreased appetite, abdominal pain, nausea, vomiting and joint pain. Approximately 20% of those experiencing symptoms will also show signs of jaundice.

Diagnosis: Confirmation of a diagnosis of HCV infection occurs in two stages. The first, a blood test, identifies anti-HCV antibodies and infection with the virus. Because of the virus's high clearance rate, however, an additional test is generally required to confirm whether the infection has become chronic. Confirmatory tests include recombinant immunoblot assay (RIBA) tests (also known the "Western Blot" test) and now, more commonly, quantitative and/or qualitative polymerase chain reaction (PCR) tests, which search for viral RNA, signifying an active viral infection.

Treatments

Currently, no vaccine is available for HCV. Because up to 20% of HCV infections resolve spontaneously, doctors often delay starting treatment for up to four months after the initial diagnosis.

If, however, the infection does not resolve spontaneously, treatment commences with the goal of establishing a Sustained Viral Response (SVR). An established SVR means that HCV is undetectable in the patient six months after treatment is concluded. Over 95% of hepatitis C patients who achieve SVR remain HCV RNA-negative long-term.



For acute hepatitis C, the standard treatment is six months of low doses of interferon. For chronic hepatitis C, until recently, the standard treatment regime for the most prevalent genotypes (1, 2, 3 and 4) was combination antiviral therapy, using peginterferon and ribavirin for between 24 to 48 weeks, depending on patient response.

This regime generally results in SVR for the approximately 40% to 50% of HCV patients who complete it. Unfortunately, many patients do not complete treatment. This occurs for a variety of reasons, including: side effects of the drugs, which makes them difficult for some patients to tolerate; the length of the treatment; and the need for strict medical supervision and monitoring over the complete period of therapy. In some countries, reduced availability of or access to interferon, due to its high cost, can also be a factor.

Over the past several years a new family of drugs known as **protease inhibitors** has emerged, which has led to significant changes in the treatment of hepatitis C.

In 2011, Victrelis (boceprevir) and Incivek (telaprevir), the first generation of these new drugs, were approved by U.S. and European regulators for treatment for chronic hepatitis C genotype 1. These protease inhibitors were quite expensive: boceprevir cost $14,800 for a 28-day supply and telaprevir, $58,000 for a 30-day supply. These costs were in addition to the already high expense of traditional standard treatments, as these protease inhibitors had to be used in combination with peginterferon and ribavirin.

The treatment period for these protease inhibitors was 12 weeks, and it was expected that SVR could be achieved in up to 80% of patients who completed treatment.

Incivek was discontinued as of October 2014, and Merck announced in January 2015 that it will discontinue the manufacture and distribution of Victrelis by December 2015, to ensure those who are using the drug in very long-term treatment plans will be able to complete treatment.

In late 2013, two new drug therapies received their first approvals to treat chronic hepatitis C. The first, Olysio (simprevir), a second-generation protease inhibitor, was approved to treat chronic hepatitis C genotype 1. The second, Sovaldi (sofosbuvir), is a **polymerase inhibitor** and a direct-acting antiviral, and was approved for treatment of hepatitis C genotypes 1, 2, 3 and 4.

Both of these drugs are also only effective if used in combination with traditional peginterferon-ribavarin therapy.

Treatment regimes utilizing these two drugs will vary by genotype, previous treatment, progression of the disease and co-morbidities.

Costs for these drugs are significant: Olysio is $48,644 and Sovaldi, $61,600 for a 28-day supply. The treatment period is 12 weeks, with the expectation that SVR can be achieved in more than 80% of patients completing treatment.

Recently, two new combination medications were approved for treatment of chronic hepatitis C genotype 1 that do not require the addition of interferon. The first, Harvoni, was approved in late 2014. It combines ledispasvir, a newly-developed NS5A inhibitor, and sofosbuvir in a once-daily tablet. The treatment course for Harvoni is 12 weeks and costs $69,300 for a 28-day supply.

A second combination therapy, Viekira Pak, consists of two pills taken together as a single dose. One pill is a combination of three agents – ombitasvir and paritaprevir, both protease inhibitors, and ritonavir, an NS5A inhibitor – and the other pill is dasabuvir, a polymerase inhibitor. Viekira Pak's treatment course is between 12 and 24 weeks, and a 28-day supply costs $45,826.

Claims Considerations

As each health insurance policy has unique benefits, policy terms and conditions, claims assessors should consider the following questions:

Is the condition covered?

The drugs discussed in this article are used to treat chronic hepatitis C, a condition which may be excluded from cover by common policy conditions or exclusions such as:

- **Pre-existing medical conditions**. HCV may be present for extended periods of time before detection as initially the condition is often asymptomatic. If it is not picked up in routine annual health screenings,

Name	Type of Drug	28-Day Cost*	Treatment Length
Victrelis (discontinued)	First-generation protease inhibitor	$14,800	12 weeks
Incivek (discontinued)	First-generation protease inhibitor	$58,800 (30-day supply)	12 weeks
Olysio	Second-generation protease inhibitor	$48,644	12 weeks
Solvaldi	Nucleotide analog polymerase inhibitor	$61,600	12 - 24 weeks
Harvoni	Combined oral pill	$69,300	12 - 24 weeks
Viekira Pak	Combined oral pill (protease and polymerase inhibitors)	$45,826	12 - 24 weeks

**Drug costs quoted are U.S. reasonable costs.*

it may not be detected until symptoms occur and are investigated. The actual infection may therefore predate the policy and, depending on policy language and need for disclosure, the condition and its treatment may not be covered.

- Some policies exclude or limit cover for all chronic conditions. As these drugs treat chronic hepatitis C, cover for treatment may not be available or may be limited.

Is the prescribed treatment medically appropriate?

- These drugs are effective and licensed for the treatment of genotype-specific forms of chronic hepatitis and should not be used for other genotypes. Ensure the claimant has the specific genotype form of the condition for the prescribed treatment.
- Depending on prior treatment and comorbidities, these newer drugs need to be used in specific combinations with other, older drugs. Ensure the prescribed regime appropriate, and that it takes into account all variables.

RGA, in association with our partner Advanced Medical Strategies (AMS), has developed treatment guidelines for hepatitis C, available upon request to treaty clients, that provide information and guidance about the disease and the medical appropriateness of each drug.

Underwriting Considerations

The primary consideration when underwriting an applicant who discloses hepatitis C is the applicant's current HCV status. Coverage and loading decisions should be based on whether the applicant has an acute or chronic HCV infection, has recovered (whether due to treatment or spontaneously), and has achieved SVR. RGA currently recommends declining any applicant with an active HCV infection (whether acute or chronic) or who is currently undergoing treatment. Further details may be found in RGA's Global Underwriting Manual (GUM).