Evolving the Treatment of Hepatitis C:
Subsidised Access to Sofosbuvir and Simeprevir is the Next Step!

Submission to the July 2014 meeting of the Pharmaceutical Benefits Advisory Committee

Submitted by: Hepatitis Australia Inc.

Hepatitis Australia, incorporated in 1997, is the peak community organisation to progress national action on issues of importance to people affected by hepatitis C. Our mission is to provide leadership and advocacy on viral hepatitis and support partnerships for action to ensure the needs of Australians affected by, or at risk of viral hepatitis, are met. Our members consist of the state and territory hepatitis organisations and other key services providing hepatitis services.

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Key Arguments for the PBS Listing of Sofosbuvir and Simeprevir

The treatment of hepatitis C infection continues to evolve, and gaining access via the Pharmaceutical Benefit Scheme (PBS) to sofosbuvir and simeprevir to be used alongside interferon therapy is the next important step in the transformation of hepatitis C treatment.

Longer term, it is likely that virtually all people living with chronic hepatitis C will be able to be cured, regardless of their genotype or co-existing health problems, by taking oral medicines with minimal side-effects for just a few months. Not everyone with hepatitis C is aware yet of the revolution in hepatitis C treatment that is occurring. Among those that are aware, some will prefer to wait for interferon-free therapies to become available rather than pursue treatment now. Others following clinical assessment may be urged to have treatment as soon as possible due to their stage of liver disease and risks to their health. For many, the treatment decision is more complex. We know from research that the personal impact of chronic hepatitis C goes well beyond the virus itself, and for some, the non-clinical aspects of a hepatitis C infection are the most significant and debilitating of all. Therefore, determining the best time to undergo treatment will often involve people weighing up the impact of not only clinical factors but also a range of personal, social and psychological factors which are specific to their own particular circumstances.

Despite having a high diagnosis rate of over 80 per cent, treatment rates are currently inordinately low in Australia at just 1 per cent in 2012. The side-effects of pegylated interferon and ribavirin are cited in the research as a major reason for this low level of treatment. Simeprevir or sofosbuvir will continue to require the use of pegylated interferon and ribavirin across most genotypes, but for a much shorter period. Treatment will therefore become much more tolerable.

Shorter and simpler treatments with much higher cure rates provide a benefit not only to individuals but also to the Australian healthcare system. The throughput in hospital liver clinics can be increased and/or treatment can be moved out of hospitals into less expensive and more convenient liver clinics in community settings. Once a cure is achieved, the requirement for intensive long-term clinical and social support is considerably reduced.

Hepatitis Australia recognises that the dollar value of achieving a cure for hepatitis C infection is significant, however we believe that the economic, health and personal cost of not achieving a cure is far greater. It is therefore the position of Hepatitis Australia that no person with chronic hepatitis C should be excluded from access to the latest and most effective treatment available. Treatment decisions must be left to the person with hepatitis C in consultation with their treating doctor having consideration for the clinical urgency to treat, as well as other personal, social and psychological factors particular to the individual.

It has been mooted that restricted access to these new high cost treatments may be imposed based on stage of disease, Hepatitis Australia strongly opposes this suggestion. Australians must not be made to wait until they actually develop significant liver disease before they can access the most effective treatment options to cure their hepatitis C infection.

Once someone has developed cirrhosis their chance of developing liver cancer is 1-3 per cent per year regardless of whether hepatitis C treatment has resulted in a cure. Liver cancer due to viral hepatitis is already the fastest rising cause of cancer death in Australia. Hepatitis C is already estimated to be responsible for more than 500 deaths each year and
unless treatment rates are increased this is set to rise by over 230 per cent by 2030. To require anyone to wait until they have moderate or significant liver disease before they can access curative treatment for hepatitis C is, in our opinion, unconscionable and will be actively opposed by Hepatitis Australia as a matter of principle.

Averting avoidable deaths remains a key goal of treatment; however, restricting treatment access solely to those in most clinical need is flawed. A number of factors point to the inherent dangers of this approach. Firstly, progression of hepatitis C is not linear or predictable at the individual level. Secondly, there is no system in place to ensure all 230,000 people with hepatitis C receive a regular liver assessment. This would be essential to track progression of their liver disease and support treatment decisions based on clinical urgency. Lastly, such an approach ignores all the valid non-clinical reasons individuals have for undergoing treatment at a particular point in time. In the view of Hepatitis Australia, determining the best time for hepatitis C treatment should remain a matter to be determined by the person with hepatitis C in conjunction with their treating doctor.

Broadly, the new treatments which are now emerging have good safety profiles. In this context, imposing any PBS restrictions other than those required for safety reasons, could be viewed as a proxy methodology for the Pharmaceutical Benefits Advisory Committee and/or the federal government to ration access to curative hepatitis C treatment.

Hepatitis Australia strongly encourages the Pharmaceutical Benefits Advisory Committee to recommend the listing of sofosbuvir and simeprevir on the Pharmaceutical Benefits Scheme to make these new medicines available to Australians living with chronic hepatitis C as soon as possible. For Australians to benefit from the new hepatitis C treatments a focus is needed on dismantling the existing barriers to treatment and in making new treatments available quickly, rather than imposing more obstacles. The PBAC committee and the government should be acutely aware that they have the potential to commence the process of turning around the hepatitis C epidemic in Australia by providing access to these new medicines without delay. It is rare to be handed the means to change the course of disease. Australia must make the most of this opportunity for the benefit of all those living with hepatitis C.

Hepatitis C in Australia

Hepatitis C is one of the most common notifiable diseases in Australia. Of those exposed to the virus, 75% go on to develop a chronic hepatitis C infection. The risk of progressive hepatitis C-related liver disease increases with the duration of chronic infection. The morbidity and mortality associated with hepatitis C-related liver disease is increasing.

At the end of 2012, there were an estimated 230,000 people living with chronic hepatitis C infection in Australia: one-third of whom have moderate to severe liver disease.

The burden of liver disease caused by the hepatitis C virus, including liver cirrhosis, liver cancer, liver failure and the potential need for liver transplant is continuing to rise. Chronic hepatitis C was estimated to be the underlying cause of liver disease in 22% of liver transplants in Australia during 2012.

Deaths from primary liver cancer in Australia are rising faster than for any other type of cancer, having tripled between 1982 and 2007. Untreated hepatitis C and untreated...
hepatitis B infections are the major drivers of this rise in mortality\textsuperscript{4}. The annual number of hepatitis C liver disease-related deaths, estimated to be 530 in 2013\textsuperscript{1}, had surpassed mortality related to HIV by the year 2000 and has continued to rise since\textsuperscript{5}.

There were a total of 10,114 new cases of hepatitis C infections diagnosed in 2012\textsuperscript{2}. Due to lack of symptoms at the time of infection, many had acquired the virus some years previously. Reported cases of newly acquired infections of hepatitis C account for less than 5% of total cases. However, the number of diagnoses of newly acquired hepatitis C infections has gradually increased from 365 in 2008 to 466 in 2012\textsuperscript{2}.

Despite having a high diagnosis rate at over 80%, Australia has a very low treatment rate. The estimated number of people receiving treatment for hepatitis C through the Highly Specialised Drug Program declined from a peak of 3,397 in 2009 to 2,360 (1%) in 2012\textsuperscript{2}. Those who achieve a sustained virological response following hepatitis C treatment are considered to be cured. However, among those who already have cirrhosis, 1-3%\textsuperscript{6} will continue to be at increased risk of liver cancer despite having achieved a cure for their hepatitis C infection.

Hepatitis C is a blood-borne virus and approximately 90% of newly acquired hepatitis C infections and 80% of prevalent cases in Australia are a result of unsafe injecting drug use practices. Within the population of people who inject drugs, those at particularly elevated risk of hepatitis C are females, those with a history of incarceration, and Aboriginal and Torres Strait Islander peoples. Of the people who acquired hepatitis C infection due to unsafe injecting drug use practices, approximately one-third currently inject drugs and two-thirds no longer do so\textsuperscript{7}.

The burden of disease is also higher among people born overseas in endemic areas, particularly in Asia and parts of Africa and Southern Europe\textsuperscript{8}. The risk of mother to child transmission is around 5-6%: other risks include receipt of contaminated blood or blood products, unsafe tattooing or body piercing and breakdowns in infection control procedures in healthcare settings. Heterosexual transmission is rare; however, more recently, some cases have been attributed to unprotected male-to-male sexual activity involving men co-infected with HIV and hepatitis C. There is no vaccine for hepatitis C and previous infection does not provide immunity to re-infection.

**Current Treatment for Hepatitis C.**

The most common hepatitis C genotypes in Australia are genotype 1 (54%) and genotype 3 (37%). Each of the other genotypes (2,4,5 and 6) has less that 5% prevalence in Australia.

**Treating hepatitis C genotype 1.**

Traditionally, treating hepatitis C genotype 1 using interferon based therapy necessitated longer treatment duration, and produced a lower cure rate in comparison to similar treatment for hepatitis C genotype 3. Following the introduction of treatment with the first generation protease inhibitors (boceprevir and telaprevir) in April 2013, treatment duration was shortened for many people and cure rates improved to a roughly similar level to genotype 3.

Current treatment for hepatitis C genotype 1 combines weekly interferon injections with daily ribavirin tablets, and a course of daily boceprevir or telaprevir tablets.
Treatment regimen with boceprevir includes:

- pegylated interferon and ribavirin only for the first 4 weeks, then
- pegylated interferon, ribavirin and boceprevir for 24 to 44 weeks

Treatment regimen with telaprevir includes:

- pegylated interferon, ribavirin and telaprevir for the first 12 weeks, then
- pegylated interferon and ribavirin is continued for an additional 12 to 36 weeks

It must be noted the time required to complete treatment depends on the person’s treatment history and how well they respond to treatment in the initial stages. Access to sofosbuvir and simeprevir will improve this for most people.

Treating hepatitis C genotypes 2 and 3.
Treatment for hepatitis C genotype 2 and 3 has remained unchanged for many years. This involves a combination of weekly pegylated interferon injections and daily ribavirin tablets over a period of 26 weeks.

Adverse side-effects of current treatment.
The side-effects from current treatment regimens, which include interferon, can be significant, and are one reason why treatment rates are so low in Australia.

Side-effects related to pegylated interferon and ribavirin include mild to severe mood disturbances; anaemia; slow blood-clotting; fatigue; flu-like symptoms; dry skin, rash; insomnia; decreased appetite; weight loss and hair loss. Often, tolerance of treatment reduces the longer the treatment lasts. Shortening the duration of treatment is important to maintain compliance with the treatment regimen.

Additional side-effects related to boceprevir include anaemia (which can be severe) and a change in taste. Additional side-effects related to telaprevir include rashes (which can be severe) and anal pain/itch. Occasionally, treatment may need to be stopped to avoid progression of significant life-threatening side-effects; this is more common in people with advanced liver disease.

Adverse drug interactions are also common. For people who have other concurrent conditions, sometimes associated with being older, this can make clinical management complex. Opportunities to reduce the length of treatment and the eventual removal of interferon would improve the management of co-morbidities in people with hepatitis C.

Cure rates.
An average 70% to 80% cure rate is achieved with current treatments among those who take the prescribed medicines as instructed by their doctor. However, there are many personal factors and comorbidities that influence treatment outcomes:

- People in the early stages of liver disease generally have higher cure rates.
- People with hepatitis C genotype type 1 with a ‘CC’ result from an IL28B blood test are more likely to achieve a cure.
- Pre-menopausal women tend to respond better to treatment than men or post-menopausal women.
- People with fatty liver disease, heavy alcohol consumption or co-infection such as with hepatitis B or HIV may have a reduced chance of achieving a cure.
Treatment with Simeprevir.

Simeprevir is a new direct-acting antiviral hepatitis C treatment (second generation NS3/4A protease inhibitor), which can be used in the treatment of hepatitis C genotype 1 infection. It is a once-a-day tablet, which is used with pegylated interferon and ribavirin.

If approved, it would serve as a replacement for the existing treatments with boceprevir and telaprevir (first generation protease inhibitors), which are also combined with pegylated interferon and ribavirin for the treatment of people with genotype 1 infection.

Clinical trials have shown:

- In people with genotype 1 infection who have not had treatment previously, cure rates of around 80% are achieved with simeprevir when combined with pegylated interferon and ribavirin taken over 24 weeks.
- In people with genotype 1 infection, who have previously undergone treatment, the use of simeprevir in combination with pegylated interferon and ribavirin produces similar cure rates to telaprevir combined with pegylated interferon and ribavirin.
- Simeprevir has a better safety profile overall compared to telaprevir and notably less serious complications resulting in a need to stop treatment.

The advantages of using simeprevir over existing treatment plans for genotype 1 infection are associated mainly with safety, tolerability and ease of use:

- Treatment is safer – fewer complications;
- Treatment is easier to take – one tablet once a day and no fatty food requirements;
- Treatment is better tolerated – fewer side-effects; and
- Treatment duration can be reduced for most people.

One disadvantage of Simeprevir is that it is not recommended for use in people who have previously been treated with pegylated interferon and ribavirin and either boceprevir or telaprevir. This is because there is no data to suggest that there would be a clinical benefit.

Treatment with Sofosbuvir.

Sofosbuvir is another new, direct-acting antiviral treatment (nucleotide polymerase inhibitor) that can be used to treat all genotypes of the hepatitis C virus. It is a once a day tablet which is combined with other medicines.

Clinical trials have shown:

- In genotypes 1, 4, 5 & 6, the use of sofosbuvir combined with pegylated interferon and ribavirin over 12 weeks produced higher cure rates than current treatment options (around 90%).
- In genotype 2, the use of sofosbuvir combined with ribavirin (no pegylated interferon) for 12 weeks produced higher cure rates than current treatment options (around 90%).
- In genotype 3, the use of sofosbuvir combined with ribavirin (no pegylated interferon) for 12 weeks produced similar cure rates to current treatment options. Two further clinical trials using firstly, sofosbuvir combined with ribavirin (no pegylated interferon) for 24 weeks and secondly, sofosbuvir combined with pegylated interferon and
ribavirin for 12 weeks are being conducted with the expectation that cure rates close to 90% can be achieved.

- Across most genotypes the cure rate also improves significantly for people who already have existing cirrhosis.

The benefits of treatment with sofosbuvir for people living with hepatitis C include the following:

- The use of pegylated interferon (which has significant side-effects) can be considerably reduced and in some cases eliminated.
- The chance of achieving a cure improves to around 90% for most people and also significantly improves for people with cirrhosis
- Side-effects are few – it is well tolerated
- The safety profile in clinical trials is good and drug interactions are unlikely to be a significant issue.

What would access to simeprevir and sofosbuvir mean for people living with hepatitis C?

The arrival of the second phase of new generation treatment of hepatitis C is a significant step forward in the journey towards curing hepatitis C. Not only will the introduction of simeprevir and sofosbuvir, as new treatment options, offer an improved experience for people who choose these over existing treatments, they increase the likelihood of a cure for more people.

Current treatment is complex, long and carries significant adverse side-effects. The new medicines allow shorter and simpler treatment with fewer side-effects. Until such time as new interferon-free regimens become available, simeprevir and sofosbuvir will continue the important transformation of hepatitis C therapy.9 10 11 12 13

One of the new treatments works across all genotypes of hepatitis C and can cure up to 9 out of 10 patients.9, 10. This means it will be possible for all patients diagnosed with chronic hepatitis C infection to be treated with the new therapies.10, 13

Effectively, treating hepatitis C and preventing HCV-related complications will free up precious health resources available to treat other diseases.

Curing hepatitis C will reduce the risk of developing life threatening liver diseases including liver cancer and reduce the costs associated with treating HCV-related complications such as cirrhosis or the need for a liver transplant.12, 13, 14, 15

Enabling access for all people living with hepatitis C to more effective treatments and a cure will allow better management of other conditions people experience as they get older.

As well as having potentially life threatening consequences, if left untreated, hepatitis C can affect a person’s social wellbeing, their ability to work, their relationships and their psychological health.13
References


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