BC Pharmacare Submission regarding Technivie™ from
HepCBC Hepatitis C Education & Prevention Society
February 16, 2016

1) Conf. of eligibility: YES

2) Patient Group Name & name of representative completing this questionnaire:
HepCBC Hepatitis C Education and Prevention Society.
Representative completing questionnaire: redacted

3) Organization's Address #20-1139 Yates St. Victoria, BC

4) Postal code V8V-3N2

5) Conflict of Interest Y/N = Y

6) Describe conflict of interest
HepCBC Hepatitis C Education & Prevention Society has received funding for hepatitis C-oriented projects such as publishing educational materials, organizing educational forums, attending and presenting at educational conferences, advertising in newspapers (events and hepatitis C patient awareness), and holding awareness activities from the following pharmaceutical companies over the last four years: Merck Pharmaceuticals, Hoffman-LaRoche, Vertex Pharmaceuticals, Gilead Sciences, Janssen Pharmaceuticals, Bristol Myers Squibb, Boehringer-Ingelheim, AbbVie, and Lupin Pharmaceuticals. In addition, both of the co-authors of this report have attended several educational conferences and meetings for which registration and travel expenses were funded by the pharmaceutical companies listed above.

7) Read PharmaCare info sheet? YES

8) Describe how the condition or disease for which this drug is used affects the day-to-day life of patients in your group.

HepCBC: Chronic hepatitis C can affect the patient in a variety of ways. In many cases there are no obvious symptoms for many decades, while the virus is "silently" destroying the liver; or the symptoms may be mistaken for some other disease such as fibromyalgia or chronic fatigue. Those with undiagnosed hepatitis C remain unaware of lifestyle changes that could slow the progression of the disease (e.g., ceasing to drink alcohol), they will obviously remain unaware that they have a serious but treatable disease, or that they are in danger of passing a serious disease to others (especially if they engage in high risk activities, e.g., MSM; PWIDs etc.). For others, the symptoms are very apparent and debilitating. In these situations, doctors are more likely to pursue active testing/monitoring and suggest treatment. Moreover, there are many sufferers who either failed the old dual combination treatment (PegINF/RBV) or chose not to try. They may be suffering silently, thinking there is no option when in fact there are highly effective cures available (albeit at significant cost which still preclude treatment options

for some sufferers). HepCBC works hard to get the message across that those in high-risk groups, but without high-risk behaviours (e.g., baby boomers) should have a one-time screening test. We also reach out to the already-diagnosed to let them know that hepatitis C is now a very curable disease.

Besides the physical symptoms, there are many hidden ways chronic hepatitis C affects sufferers' daily lives. One common manifestation of hepatitis C is depression. Depression kills, and can ruin relationships along with joy. Another common manifestation, "brain fog" or cloudy-thinking stifles concentration and clarity, slowly progressing along the spectrum to encephalopathy. Many experience fear of future disability and inability to support self and family, especially if their caregiver must curtail his/her own employment to look after the sick family member. Many sufferers fear the loss of relationships, housing, or job due to commonly-held stereotypes and stigma against those with hepatitis C or the fear that the sheer toll relatives experience caring for a sick family member will drive people away. It is a very isolating disease. In addition, many relatives of hepatitis C sufferers have already experienced the loss of a loved one to the disease and continue to experience loss and distress both emotionally and financially because of the premature passing of a close family member.

Sufferers of hepatitis C report a variety of physical and mental manifestations of the disease. The most common that we regularly hear about from those afflicted who seek support, advice and guidance from our group, are listed below in general order of severity. These manifestations cover a diverse range of effects, demonstrating that the consequences of hepatitis C for an individual can be devastating. Manifestations/symptoms can broadly be divided into two categories: Physical and mental, although there is significant overlap between the two:

- Psychological trauma of living with a stigmatised illness
- Feeling "unclean" with anxieties over infecting others
- Fear of or trauma from harsh interferon-based treatments
- Fatigue
- Depression
- Hopelessness and despair of ever being able to eradicate the illness or to feel well again
- Frequently having to compensate, modify or avoid activities due to hepatitis C (both physical and social)
- Thyroid problems
- Stomach problems
- Arthritis
- Diabetes
- Fibromyalgia
- Ascites
- Varices
- Cirrhosis
- Liver cancer
- Liver transplant

9) If the patients in your group have tried the drug under review, please tell us about the effects they experienced.

HepCBC: We do not have any patients within our groups who have been treated with the drug combination of Technivie™ under review. However, we have three patients within our group who were treated with Holkira Pak™, two in the context of a trial. Since the components of Technivie™ are identical to Holkira Pak™, except that Technivie™ does not contain dasabuvir, it is fair to suggest that patient experiences of Holkira Pak™ can be a guide to the likely experience of a patient on Technivie™. While we have included the experiences of two of these patients in our submission for BC PharmaCare's review of Holkira Pak™, we decided to include them in this current review.

The first patient, a male in his 60s who is cirrhotic, had unsuccessfully gone through two treatments before finally achieving SVR nine months ago with Holkira Pak™. He was in extreme pain and suffering from severe fatigue and brain fog before the treatment started. He had this to say:

"I had ribavirin with the Holkira Pak™. Not a single side effect that I am aware of. I was very sick when I started and within days began feeling better. Within a week the pain had dissipated and confusion was replaced by euphoria."

The second patient, a male aged 58, took part in a trial where all those on the trial achieved SVR. He was extremely enthusiastic about the drug combination, despite having to take ribavirin. He had this to say:

"I had cirrhosis (Fibroscan 35 kPa), and was in an AbbVie 3D clinical trial called Turquoise II with ribavirin. I took these drugs for 24 weeks and there was shortness of breath. The ribavirin made it hard to sleep and focus at times, but other than that, the trial was a piece of cake. I did not experience any of these (side-effects) from the AbbVie drugs, but the ribavirin does make you anxious at times right after taking it, and sleep was a problem at times. I understand that ribavirin may not be used for all treatments. So without ribavirin, the patient would have an easy time on this combination. What people need to look at is the proven success rate of this combo versus the average success rate of the old treatment, and then factor in the lasting damage the interferon can have on your system, and using the AbbVie drug is a no brainer."

"A lot of people who have done the old treatment have had to repeat it, at great risk to their health and a huge cost to the medical system. In contrast, this (AbbVie) treatment cures almost everyone. In the trial I was in there were ZERO relapses. I have been free of the virus since November, 2013 and my last Fibro Scan reading has now dropped from 35 down to 20 kPa."

The third patient, a woman, aged 60, was infected with Hepatitis C, genotype 1a, via a blood transfusion more than 30 years ago. The main effect of her disease was fatigue, although fortunately she had little disease progression. She was enrolled in a clinical trial with the AbbVie drugs that comprised Holkira Pak™, tested "undetectable" for the virus after four weeks and achieved SVR. She gave us this information:

"I was on a double blind clinical trial. After 12 weeks of treatment I found out I was the 1 out of 4 on the placebo. Then I continued on the 'real' treatment for 12 more weeks and was cured. During the first 12 weeks on the placebo I was extremely tired. During the second 12 weeks on the 'real' thing I was good. It [Holkira Pak™] should be covered. It is always far cheaper to be pro-active and treat patients, rather than pay for all the medical complications that affect the majority of infected hepatitis C patients."

As we know, BC Pharmacare has taken on board these (and other) patient experiences and added Holkira Pak™ to the formulary. It would seem logical, therefore, to include Technivie™ for genotype 4 as well.

10) What drugs or other treatments have the patients in your group used, or are they currently using, for the condition or disease for which this drug is used? *Please list all of the drugs and tell us about the experience of the patients in your group with each treatment.*

HepCBC: patients in our group have undergone treatment for hepatitis C with a variety of drug combinations. Over the years, these combinations have ranged from interferon only, followed by peg-interferon plus ribavirin, or fairly recently (2011-2013), the dual combination of peg-interferon plus the addition of a 1st generation protease inhibitor (either boceprevir or telaprevir) or occasionally with a 2nd generation PI (simeprevir). The more recent treatments (prior to the approval of sofosbuvir), have been limited to those with genotype 1. In addition, these DAAs both compounded and increased the range of adverse effects caused by interferon. During the time they were used as "Standard of Care," there were sometimes life-threatening events (e.g., severe anaemia, low neutrophil counts, many drug/drug interactions, etc.). These negative factors, together with an extremely high pill burden and very rigid dosing schedules, for both boceprevir and telaprevir, meant these treatments had a high drop-out rate. Although these two drugs aided the cure of many patients with genotype 1, we are fortunate that they were superseded relatively quickly with the new DAAs.

Over the decades there have been many treatment failures, particularly on dual therapy (peg-interferon/ribavirin), and primarily amongst genotype 1 patients. Peg-interferon and ribavirin produce difficult side effects in most patients (e.g., influenza, symptoms, anaemia sometimes leading to blood transfusions or cardiac arrest, inability to work or care for oneself, etc.). Even more concerning is the fact that the effects of interferon treatment seem to continue for the majority of patients well after the end of treatment, even (in some cases) permanently. These include often serious and long lasting disorders (e.g., thyroid disorders, peripheral neuropathy, arthritis, etc.). Many patients, whether they achieve SVR or not, report feeling worse than before treatment. By contrast, those from our group who have been fortunate enough to be treated or re-treated with interferon-free regimes report far fewer side effects. No-one has yet reported long-lasting or devastating consequences like those experienced following treatment with interferon (although we are aware further side effects could emerge as these new combinations are increasingly used). We are pleased that, as further new agents become added to the BC PharmaCare forumulary, interferon (and ribavirin as well) become used far less frequently. We hope that these two drugs can be entirely replaced eventually, even for those with difficult-to-treat characteristics (e.g., genotype 3 with cirrhosis). In addition, we are aware that the number of sufferers now being given access to the new drugs is growing, following BC PharmaCare approval of some of the new agents. Without doubt, these treatments have been not only far more effective, but immeasurably easier to tolerate as well.

However, none of the new treatments approved in BC have specifically targeted genotype 4 as Technivie™ is designed to do. Numbers of sufferers of this genotype may be small (in relative terms) across North America, but they still run in to the tens of thousands (see section 11 below).

11) Please tell us why your organization believes this drug should be included in the BC PharmaCare program.

Let us start with the words of a patient from our group which helps provide a rationale for the inclusion of Technivie™ to the BC PharmaCare formulary: "If Sovaldi™ and Harvoni™ are going to be available to so few people through BC PharmaCare because of the high cost, something else that doesn't include Interferon has to be offered to those of us who have been suffering for so many years and don't fall into Pharmacare's priorities (i.e., have an unusual combination of genotypes and a low risk of transmission to anyone else)."

Overall, HepCBC remains enthusiastic about the current new treatments that are being considered by BC PharmaCare. However, as we are all aware, there is by no means a perfect drug, or "one size fits all" solution which can be prescribed for all hepatitis C sufferers. Hepatitis C is a diverse and complex virus, and so we welcome the chance to approve several new agents, so that they can be prescribed in varying combinations. In this way, doctors will be able to "tailor" treatments and prescribe according to each patient's individual circumstances. For this reason, HepCBC would like to see the approval of Technivie™ to treat genotype 4.

HepCBC believes that there is certainly a gap in treatment options for the less common genotypes in Canada. The percentage of sufferers infected with genotype 4 worldwide is approximately 8.3%. [(1)] While much of the concentration occurs in Middle Eastern countries, the estimated number of sufferers in North America is around 55,000 which accounts for approximately 1.2% of infections in this region.[(1)] These numbers are not small, even if they appear to be in terms of overall percentages of HCV infection in North America. Moreover, increased global mobility means that the less common genotypes that we see in Canada (such as genotype 4) can and will travel. We already know that European countries are starting to see an increase in numbers of those infected with G4. Regarding Canada specifically, in addition to economic migration, a very current event we are witnessing globally, is compassionate migration in the form of the movement of Syrian refugees to many countries. The infection rate is Syria is estimated to be between 1%-2% of the population.[(2)] Therefore, it is fair to suggest the possibility that the countries with significant Syrian refugee intake may well see a rise in numbers of those affected with hepatitis C, genotype 4. These countries could include Canada as it meets its obligations with respect to the current crisis. While we are in no way suggesting that these groups are likely to transmit the virus to Canadians and other residents (as Syrians are likely to have been infected via the medical system in Syria rather than being PWIDs), we are raising the possibility of a potential rise in numbers of G4 sufferers in Canada over the coming years. Current G4 standard of treatment with peg-interferon and ribavirin, yields success rates of between only 43% to 70% for a 48 week course of treatment.[(3)] It is also possible for G4s to be treated with Sovaldi™ plus peg-interferon + ribavirin, or, alternatively, with sofosbuvir plus daclatasvir ±ribavirin. However in BC, these treatments are unavailable under the BC PharmaCare Program.

Thus, the approval of ombitasvir, paritaprevir and ritonavir (± ribavirin) would provide better treatment options for G4 with stellar SVR rates of between 91%-100%. [(4)] Cutting treatment time down to some 25% of what it has been thus far while increasing cure rates to between 91% and 100% provides a clear rationale for approval. Finally, Technivie™ has been demonstrated to be safe and effective with few adverse effects or even side effects.[(5)] Therefore, it seems likely that in the absence of any complicating factors, an all oral treatment regime for a relatively short period of time will require less clinical management, hospital visits, less (or no) time off work, etc.

Furthermore, we believe that the more 'competitors' there are to Gilead's Sovaldi™ and Harvoni™ (which can both be prescribed for genotype 4) will mean that prices for all these effective new options

will (or at least should) be substantially reduced. As Abbvie's Holkira Pak™ provides an excellent alternative to sofosbuvir-containing regimes for some genotype 1 patients, it seems logical to conclude that Technivie™ for genotype 4 should also be included in the BC formulary.

Finally, HepCBC continues to campaign vigorously for treatment to be made available universally. Treatment is more successful the earlier it is initiated, but there is a current minimum threshold (throughout most of Canada including BC) of fibrosis level 2, which is determined by liver biopsy, Fibroscan, or other non-invasive means. However, by the time patients reach the F2 threshold, significant liver damage has already occurred. Once hepatitis C becomes chronic, it is almost never going to spontaneously go away. It can only get worse. It is likely that patients will suffer a reduced quality of life, and be more susceptible to serious diseases such as liver (and other) cancers. They are always at risk of inadvertently infecting others, especially if they are unaware that they have the disease (albeit the risk is higher in some populations than in others).

It is true there might have been a rationale for withholding treatment from those without advanced disease when only the less effective, older, harsher treatments were available (on a "treatment is worse than the disease" basis). However, this is far less relevant today, when there is the very realistic prospect that all patients can be cured quickly, and relatively easily as well. At the very least, we strongly argue for a greater percentage of patients to be treated than is currently the case. In order to make a significant impact on the prevalence of chronic hepatitis C and morbidity/mortality due to the disease, modeling suggests a minimum of 6% or more per year, rather than the current 1.4%, which barely keeps up with the incidence of new cases.

Finally, equity issues resulting in treatment disparities (i.e., between urban or rural groups, or between those who have private insurance versus those who are completely dependent on BC PharmaCare) are beyond the scope of this review but something we hope will be investigated and addressed in the not too distant future.

References:

(1) Messina, J. P., Humphreys, I., Flaxman, A., Brown, A., Cooke, G. S., Pybus, O. G. and Barnes, E. (2015), Global distribution and prevalence of hepatitis C virus genotypes. Hepatology, 61: 77–87. doi: 10.1002/hep.27259

(2) Mohamed A. Daw and Aghnaya A. Dau, "Hepatitis C Virus in Arab World: A State of Concern," The Scientific World Journal, vol. 2012, Article ID 719494, 12 pages, 2012. doi:10.1100/2012/719494

(3) University of Washington (2015) Hepatitis C Online: Treatment of HCV Genotype 4: http://www.hepatitisc.uw.edu/go/treatment-infection/treatment-genotype-4/core-concept/all [accessed on 15/09/2015]

(4) Abbvie (24/07/2015) TECHNIVIE™ (ombitasvir, paritaprevir, and ritonavir tablets) Receives FDA Approval as the First and Only All-Oral, Interferon-Free Treatment for Genotype 4 Chronic Hepatitis C in the U.S. http://abbvie.mediaroom.com/index.php?s=20295&item=122629 [accessed on 15/09/2015]

(5) FDA US Food and Drug Administration (24/07/2015) FDA approves Technivie for treatment of chronic hepatitis C genotype 4: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm455857.htm [accessed on 15/09/2015]