BC Pharmacare HepCBC Submission regarding Holkira Pak™

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, and AbbVie. In addition, one of the co-authors of this report has attended several educational conferences and meetings for which registration and travel expenses were funded by the pharmaceutical companies listed above.

One of the patients (Pt 2) submitting remarks said that in February 2015, they attended an AbbVie-sponsored conference and received an honorarium for attendance. However, they have not agreed to support Abbvie's product. Their opinions are included, based solely on their experience as a hepatitis C sufferer who has been treated with an interferon-free combination.

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 are unaware of lifestyle changes that could slow the progression of the disease, are unaware that treatment could stop its progression entirely, or that they are in danger of passing a serious disease to others. For others, the symptoms are much more obvious and debilitating. In these situations, doctors are more likely to pursue active testing/monitoring and suggest aggressive treatment.

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 relationships along with

joy, and “brain fog” (another common manifestation) stifles concentration and clarity, slowly progressing along the spectrum to encephalopathy. Many experience fear of future disability and inability to support self and family, and fear of losing relationships, housing, or job due to commonly-held stereotypes and stigma against those with hepatitis C, as the patient experiences below demonstrate:

Pt. 1:

Female, 69 years old
Last biopsy in 2010: stage 3 bridging fibrosis
No co-infections
Infected by a blood transfusion in 1955 (60 years ago)
Diagnosed in 1994 (21 years ago)
Genotypes 2 and 4
Treated with Interferon in 1995 – unsuccessfully:

“Hepatitis C has affected every aspect of most of my life. I suffer from constant fatigue and lack of stamina. This prevented me from following the teaching career I had prepared for and made employment next to impossible. Lack of employment has prevented me from preparing for my "retirement" years. I am charged double for travel insurance to visit family who live in USA. I have not been able to be as involved in my husband's, children's and grandchildren's lives as I would like to have been. I don't have the stamina to travel or even to get involved in community activities.”

Pt. 2:

Female, 63 years old: “I have stage F3 liver damage. I was infected in 1982. I was diagnosed in June 2014 with genotype G1a. In May of this year I finished treatment with Harvoni and at the end of the treatment my viral load test indicated I was found to have ‘no virus detected’. During the last 30+ years I was unaware I was infected. Looking back I can see many of my symptoms, fatigue, memory problems, and muscle pains, were probably due at least in part to hep C. I always was looking for answers as to why I felt bad. When I was diagnosed last year it made my health situation understandable, and soon after starting Harvoni I experienced a sense of well-being which I hadn’t felt in a long time. The feeling of always having to ‘push’ to get through my day was gone.”

Sufferers of hepatitis C report a variety of manifestations and symptoms 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

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 have two patients within our group who were treated with Holkira Pak™, both in the context of a trial. The first (Pt3), 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 make 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." (His cirrhosis has reversed and is almost gone; the beginning of cirrhosis is approximately 17 kPa).

The second patient (Pt4), 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 on a clinical trial with the AbbVie drugs that comprise 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."

However, despite these glowing reports, it is sadly the case that the majority people with hepatitis C in BC remain untreated or have been treated unsuccessfully with harsh interferon regimes in the past. Hepatitis C sufferers are often ageing "baby-boomers", who have been infected for decades and are therefore in danger of being hospitalized due to - or dying from - hepatitis C. Thus, they are in urgent need of treatment to prevent imminent complications of severe liver disease. However, younger patients would benefit greatly from treatment in terms of quality years of life recovered. Moreover, the earlier treatment is given after contracting the disease, the more likely it is to be successful. Highly effective, easy-to-tolerate treatment options, such as those which have gained or are now gaining regulatory approval, will do much to help change this desperate state of affairs.

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 have 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. Other negative factors are that boceprevir and telaprevir have a low barrier to resistance, leading to the very real possibility, not only of treatment failure, but also to the emergence of resistant-associated variants, which may preclude future treatment options, at least for some time. Simeprevir, on the other hand, only requires one pill a day (either together with peg-interferon and ribavirin or it has sometimes been prescribed "off label" in combination with sofosbuvir). However, simeprevir has not been without its drawbacks as it is fairly ineffective for Genotype 1a sufferers who have the Q80K polymorphism (which can naturally occur in the hepatitis C virus and almost exclusively in genotype 1a), so those with the 1a subtype need to be tested before treatment starts. Finally, it would not be an understatement to say that the addition of the boceprevir or telaprevir resulted in two of the toughest treatments there have ever been (or ever will be) for hepatitis C, while not being particularly effective

for many, especially in comparison to the new generation of (mainly) interferon-free regimes, such as Sovaldi™, Harvoni™ and Holkira Pak™.

Hepatitis C patients, especially those within our group, tend to be fairly knowledgeable and well informed both about their condition, about current and possible future treatments. Many of them have either had to avoid (or wanted to avoid) treatments containing interferon and/or ribavirin and/or a 1st/2nd generation PI. By contrast, a few sufferers have had access to interferon-free treatments, either in the context of a clinical trial or (rarely) following approval (e.g. of Sovaldi™; Harvoni™; Holkira Pak™) by Health Canada. These have been not only far more effective, but also far easier to tolerate.

Over the decades there have been many treatment failures, particularly on dual therapy (peg-interferon/ribavirin), particularly amongst genotype 1 patients. This was before an understanding of how the variation in the IL28b (host) gene subtype increases or decreases the likelihood of interferon treatment success. In addition, 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.). Furthermore, and as previously noted, toxicity is significantly increased by the inclusion of one of the early PIs. 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, frequently 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 reported long-lasting or devastating consequences like those experienced following treatment with interferon. Note the contrast between the following two patient reports. The first was unsuccessfully treated with interferon and the second successfully treated with Harvoni™:

Pt. 1:
"I was treated with Interferon alone in 1995, and had to be taken off it after 5 months because of adverse side effects. The side effects were life threatening in that they included suicidal depression. I also experienced severe headaches, joint and muscle pain, hallucinations in early days, hair loss, weight loss, severe itching, debilitating fatigue, fever and insomnia. I have not been treated with Holkira Pak™, and was unaware of it until this survey."

Pt. 2:
"I have just finished a 12 week treatment with Harvoni™. I experienced very minor symptoms of headache and only in the beginning I also was sometimes lightly nauseous. I was very happy with my treatment. It did not interfere with my lifestyle in any way. The side effects were very minor. It looks as though it was successful although it is too soon to say for sure. I would have considered Holkira Pak™ had it been available when I chose to use Harvoni™ in 2014 (my treatment was planned in 2014)."

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 two of our patient group:

Pt. 1:
"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)."

Pt. 2:
"My opportunity to use Harvoni™ was at the time possible only because I have third party insurance and Gilead enrolled me in the Momentum™ program. Without this support from my insurer and Gilead I would have been unable to afford treatment. I would not have been able to afford a cure for hepatitis C. I am supporting the coverage of Holkira Pak™ because I know what a difference being treated with Harvoni™ has made to me. It has given me my life back. Having Holkira Pak™ as an affordable option along with Harvoni™ will be literally a life-saving action for people who are unable to purchase drug coverage outright or to access insurance coverage as I did. Before I knew my Harvoni™ treatment would be covered by my insurer, I was considering how I would pay for it. The only option I had was to sell my house. I couldn't imagine what would happen to my family then. I tried to imagine if my life was really worth that much or was it more important to my family to be financially stable. That was a horrible time for me. It was such a relief when my insurer said they would cover the drug and Gilead agreed to help. I don't know if you can imagine the fear I was experiencing then. People who need Holkira Pak™ deserve to be treated just as I was able to be. No one should have to make the choice that I was prepared to make.

I should have said something about how patient oriented Holkira Pak™ is and I think they would provide the best possible experience for a positive outcome for patients. (Hope that doesn't sound like I don't think Gilead does a good job too, but AbbVie really is trying hard to address patients in a personal way."

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 it is likely that a number of drugs will need to be licensed, 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 approval of DAAs individually, as has already been the case with sofosbuvir, simeprevir, daclatasvir and asunaprevir. For example (and in relation to Holkira Pak™), recent clinical trials have demonstrated a 100% cure rate for genotype 4 sufferers with a combination or three of the four components of Holkira Pak™. While genotype 4 sufferers are a minority (in Canada and elsewhere, comprising some 13% of the total number of those infected with hepatitis C worldwide[1]), they still require effective treatment options. They should not be presented with additional stumbling blocks to treatment when the individual drugs they need are available and have been shown to be both effective and safe.

As **Tarek Hassanein, MD,** professor of medicine at the School of Medicine at the University of California, San Diego, director of Southern California Liver Centers and director of Southern California Research Center, points out, those with genotype 4 respond to drug combinations such as Gilead's Harvoni™ and AbbVie's Holkira Pak™, but these combinations aren't approved by the FDA (in the US) unless the

[1] http://www.ncbi.nlm.nih.gov/pubmed/25086286 [accessed on 19/5/2015]

patient has genotype 1 infection. In our view, BC PharmaCare needs to be mindful of the kind of restrictions that can be placed on access for those who could really benefit from these treatments. [2]

We note also that Phase II trials are underway with a combination of the AbbVie drugs for genotype 3 patients.[3] We should remember that, contrary to previous thinking, genotype 3 has emerged as the most difficult genotype to treat, with characteristics such as more rapid disease progression and a tendency to other complexities such as "fatty liver". Having a range of effective drugs for doctors to choose from will no doubt assist in the treatment of this challenging population.

Whatever a patient's genotype, subtype, physical or disease characteristics, the costs of the new treatments (in this case, the current cost of Holkira Pak™) present a considerable barrier to a cure. We therefore hope that BC PharmaCare and AbbVie will be successful in negotiating a price which enables treatment to be provided universally for all patients. Moreover, we believe that another 'competitor' to Gilead's Sovaldi™ and Harvoni™ is a good indication that prices for all these effective new options will be (and should be) substantially reduced.

As referred to above, we believe treatment should be 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. Patients will suffer a reduced quality of life, and be more susceptible to serious diseases such as liver cancer. They are always at risk of inadvertently infecting others, especially if they are unaware that they have the disease.

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, we suggest a minimum of 5%-6% 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.

To summarise, patients within our group are very excited about the new treatments, especially the interferon-free combinations. However, they are sometimes confused by the plethora of new drugs currently being tested in clinical trials/becoming available and their different classes. In addition, it should be emphasised that patients are almost always concerned and disappointed by the costs of these treatments and what this means for them (that they won't have access to them because of how

[2] http://www.healio.com/infectious-disease/hepatitis-c/news/print/hcv-next/%7Be1e56feb-316a-4c64-a07c-d8a2a37c76b8%7D/hcv-genotype-4-a-global-challenge [accessed on 19/5/2015]
[3] http://www.hepatitisc.uw.edu/pdf/treatment-infection/treatment-genotype-3/core-concept/all [accessed on 19/5/2015]

expensive they are). This presents a very difficult situation: the cure is there, with no or few side effects and significantly reduced treatment durations. But the treatment is completely out of reach. HepCBC wants to encourage BC PharmaCare to approve Holkira Pak™ and make it available, in addition to Sovaldi™ and Harvoni™, but also to move towards universal treatment of those infected with hepatitis C.