BC Pharmacare HepCBC Submission regarding Gilead's Epclusa® (sofosbuvir+velpatasvir)

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, Education Project Mgr. and REDACTED, Board Secretary and Volunteer

3) Organization's Address

#20-1139 Yates St.

4) City

Victoria, BC

5) Postal code

V8V-3N2

6) Conflict of Interest Y/N = Y

7) 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, Lupin Pharma Canada, Gilead Sciences, Janssen Pharmaceuticals, Bristol Myers Squibb, Boehringer-Ingelheim, and AbbVie. 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.

8) Read PharmaCare info sheet? YES

9) 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. Many of those with undiagnosed hepatitis C are unaware that lifestyle changes could slow the progression of the disease, and that they are in danger of passing a serious disease to others. They are also unaware that treatment could stop its progression entirely. 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 other hidden ways chronic hepatitis C affects sufferers' daily lives. One common manifestation of hepatitis C is depression. Depression kills relationships along with joy. "Brain fog" (another common manifestation) stifles concentration and clarity, slowly progressing along the spectrum to hepatic encephalopathy (HE). Sufferers experience progressively debilitating symptoms others see only as personal failures. On top of this is fear of becoming a burden on family and friends as the patient experiences below demonstrate.

Patient. 1:

Before I was diagnosed, I suffered from fatigue. I didn't realize it until I was cured. I couldn't walk around Butchart Gardens. I considered using a wheel chair! I thought it was old age. Now, [this patient has been cured using a new DAA but not Epclusa®] I can walk 10 km with no problem. I used to wake up every morning with a stomach ache, and I had bad joint pains. These are all gone!

Patient 2 writes:

I'm cured now, after almost 40 years being HCV+. Diagnosed in 1992, I contracted it between 1958 (when I got a gamma globulin shot to prevent me getting the Asian flu when both my parents got it) and 1975 (when I got my second RhoGam shot after childbirth). A lifelong teetotaler, I didn't become symptomatic until 2004 or so, when I lost my ability to digest many kinds of protein, and was experiencing great difficulty concentrating and staying awake, finally having to close my mentally-demanding small business.

It [hepatitis C] has created a lot of stress for my friends and family members, especially my adult children, who still worry about me a lot, even now, after I'm cured. I think they got in the habit of worrying if I'll either die while their kids - my grandchildren - are very young, or that they'll have a big job looking after me when I'm older and ill.

The most common symptoms that we regularly hear about from those afflicted who seek support, advice and guidance from our group, are listed below, starting with psycho-social effects and ending with those most potentially life-threatening. 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 stigmatized 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

Non-liver cancers

Liver cancer

Liver transplant

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 the drug under review would be used for?

Please list all of the drugs or other treatments and tell us about their experience with each. In particular, did they consider any of the drugs or treatments to be successful and why?)

HepCBC: patients in our group have undergone a variety of treatments for hepatitis C. Over the years, HCV treatment ranged from interferon only, moving on to Pegylated-interferon (Peg-INF) plus ribavirin (side effects in most patients included influenza symptoms, anaemia, disruption of work, mood and behaviour changes, and others even more serious, including permanent thyroid disorders, peripheral neuropathy, autoimmune disorders and arthritis). There were many treatment failures, particularly on Peg-INF/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. Then, about five years ago (2011-2013), researchers presented the dual combination of Peg-INF + ribavirin plus the addition of a 1st generation protease inhibitor (PI) — either boceprevir or telaprevir — or occasionally a 2nd generation PI, simeprevir.

The addition of boceprevir or telaprevir resulted in two of the toughest treatments there ever have been (or ever will be) for hepatitis C, while not being particularly effective for many. The terrible side effects of Peg-INF, ribavirin, boceprevir, and/or telaprevir gave hepatitis C treatment a bad reputation. Boceprevir and telaprevir were phased out as far superior drugs became available, and Peg-INF use is generally confined (in combination with sofosbuvir +ribavirin) to those in which its use brings significantly greater efficacy, such as those with genotype 5, or previously-treated genotype 2/3 patients with cirrhosis. The side effects of ribavirin, still added to some treatments, seems to many patients to have become more tolerable as treatment time has significantly shortened, diminishing its cumulative effects. However ribavirin can exacerbate underlying heart disease.

Simeprevir, on the other hand, only requires one pill a day (either together with Peg-INF and ribavirin or as “off label” in combination with sofosbuvir). However, simeprevir has not been without its drawbacks, either, 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. In February, 2016, Health Canada reported a

possible link between simeprevir and liver function impairment, so it now recommends that patients with moderate to severe liver damage should not use simeprevir.

However, we are learning these kinds of problems are non-issues with the next generation of (mainly) interferon-free DAA regimes, such as Sovaldi™ (sofosbuvir), Harvoni™ (sofosbuvir+ledipasvir), Holkira Pak™(dasabuvir + ombitasvir/paritaprevir/ritonavir [+ ribavirin for genotype 1a and cirrhotics]), Zepatier™ (elbasvir/grazoprevir), and Sunvepra™ (asunaprevir)+Daklinza™ (daclatasvir) — this last combo for Genotype 1b only and with interferon/ribavirin added in some cases. Those from our group who have been fortunate enough to be treated or re-treated with interferon-free regimes report far fewer side effects. To date, we have not heard of any consequences during or following treatment like those experienced following treatment with Peg-INF. However, we have noted the recently-announced investigation by the European Medicines Agency (EMA) into HBV reactivation following DAA treatment, plus a possible link reported between DAA treatment and resurgence of HCC, and another possible link between DAA treatment of cirrhotics and rapid liver decompensation (J.H. Hoofnagle, EASL *Journal of Hepatology* 2016, vol. 64).

Below is the experience of one of our Patient Group Members who tried five treatments before being cured. These are the treatments this patient tried and the effects caused by each of them:

Patient 3 had the following five treatments:
1. Interferon alone (unsuccessful) — Weight loss, flu-like symptoms, achiness, fatigue
2. Interferon + ribavirin (unsuccessful) — As above, but worse
3. Interferon low-dose maintenance (successful in keeping the disease from progressing but no permanent cure) — Slight fatigue/achiness
4. Peg-IFN + ribavirin (unsuccessful) — Weight loss, flu-like symptoms, achiness, fatigue, but less than #2 above.
5. Daclatasvir + asunaprevir (successful) — NO side effects.

And here is the experience of another typical patient in our group, who only needed one course of treatment, but that treatment was tough and challenging:

Patient 4:
I was treated with Peg-INF, ribavirin and boceprevir in 2013. The treatment was successful and I am very grateful to be free of the threat from hepatitis C. However, it was an extremely tough 30 weeks: I could not have worked (luckily my family supported me). I spent days in bed. I was also terribly anaemic. In addition, it took me many months to recover following treatment. Although free of the disease, I still suffer lingering effects which I suspect are a result of the combination of drugs I took or of at least one of them. For example, one of my toes is numb. I also have extremely dry eyes.

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

We do not have any patients in our group who have taken the sofosbuvir+velpatasvir combo. However, data from the Astral trials, which we discussed in a webinar run by Canadian Treatment Action Coalition (CTAC), indicate not only high cure rates but fewer side effects amongst patients in the trials than in interferon-based therapy. The side effects appear to be on par with those experienced by patients on other all-oral HCV treatments. The main side effects seem to be fatigue, nausea and headache.

However, if ribavirin needs to be included, the possibility of ribavirin-induced side effects (e.g., anaemia, skin rashes, irritability etc.) should be anticipated.

12) How do you think the patients in your group could benefit from the drug under review? (For example: relief of existing symptoms; improvement in quality of life; or improvements to their condition and their long term health and well-being. Please provide details.)

BENEFITS: The two most obvious benefits to patients in our province are that those with difficult-to-treat genotypes now have an excellent DAA option, and that those with decompensated cirrhosis now have a well-tested (and usually ribavirin-free) regimen as an option. A minor benefit is that genotype testing is not required for this treatment (although it is a huge benefit in international efforts to conquer HCV).

The Astral trials show Epclusa® to be highly effective globally across all seven genotypes, including difficult-to-treat populations such as those who have G3, those who have cirrhosis, and those who have previously failed treatment (including with DAAs). SVR12 rates are at around 97%+ including high rates for G3 (95%) and those with cirrhosis (even decompensated cirrhosis). The combination was compared in the Astral trials against SOF/RBV and clearly tops that alternative, especially for G3, where SOF/RBV is not a particularly effective option.

The combination has also been trialed among those with decompensated cirrhosis (Astral 4) and shown to be effective, especially with the inclusion of RBV. Whether to use RBV involves weighing the side effects of the drug in comparison to an increase in SVR for those with more advanced liver disease. The available data seems to indicate that RBV can be avoided by most people on this regime, although RBV addition may be considered in cases where advanced liver disease is a factor.

This combination is as easy to administer and to use as all the other approved 3rd generation DAAs (usually, one pill orally per day, unless ribavirin is included). Patients undergoing this treatment are likely to be able to continue work, study or go about their daily routines. In most cases, being cured of HCV will clearly benefit a patient in terms of their overall health. The sooner it is given and the virus completely eliminated from the body, the sooner fibrosis (and even cirrhosis) damage stops and the healing can begin, with the risk of liver failure, extrahepatic manifestations, and cancer diminishing every year thereafter. The virus's long-term damage to the brain and other body systems may not be as reversible, however, giving further reason to promote expediency in treating all BC's patients, even those who are asymptomatic, before they burden the economy and healthcare system.

CONCERNS: The lack of cross-regime comparisons, and the lack of controls in most of the DAA trials have been noted as research weaknesses and gaps that widespread usage will enable researchers to address. The implication here is that patients who use DAAs, even the first year or two following coverage, are still, in a sense, "guinea pigs" — however 'noble' a role — but one we do not relish.

Although all the new DAAs appear to have fewer side effects, as their use becomes more frequent, we expect more side effects and contraindications to emerge. This is inevitable as trials are generally conducted according to stringent eligibility criteria and may exclude or not capture certain populations. As ever, we advise caution and close monitoring once the drug combination is approved in order to build

up further knowledge about it in a larger population and over a longer period of time. Monitoring will find any additional side effects which might emerge either during or after treatment, and help determine how we should respond to them.

We must also draw attention to the current investigations into reactivation of HBV and resurgence of HCC in some populations. It may be the case that it is not always the optimum choice to treat every patient immediately without due consideration of adverse consequences which might arise as a result.

We have noted the recent investigation by the European Medical Association (EMA) into the possibility of HBV reactivation among HCV patients taking the new interferon-free DAA treatments. Thus we believe that, until more information is available, patients who could be susceptible (i.e., those who have been previously infected with HBV, whether resolved or not) should be monitored closely and treatment modified appropriately. It is prudent to suggest that all HCV patients, about to embark on an all-oral regime, should have their HBV status confirmed prior to starting treatment, at least until the EMA investigation provides more data.

We also note that research has indicated a possible resurgence of hepatocellular carcinoma (HCC) following (3rd generation) DAA treatment. While this is worrying, it also emphasizes the point that treatment of HCV patients before they present with advanced liver disease is essential to minimize the risk of eventual HCC. Prior signs of HCC must be considered carefully before a treatment regimen is prescribed, at least until more data becomes available. Monitoring such patients regularly for HCC activity during treatment is essential.

Finally, the question of development of resistance continues to come up regularly, not only as a concern for individual patients who may eventually become resistant to therapies, but to the HCV+ population as a whole who may be exposed to resistant versions of the virus. Once a resistant version enters the blood system, particularly in at risk communities such as IVDU or prison populations, it can become of clear danger to the broader public health.

OUR RECOMMENDATIONS:

HepCBC recommends the inclusion of Epclusa® in the BC PharmaCare formulary as it gives doctors an **effective tool for curing hepatitis C in previously difficult-to-treat populations**. In addition, we applaud any HCV treatment such as Epclusa® with a pan-genotypic aspect. Eliminating the need for genotype testing is not only a cost-savings; it can mean **quicker, more efficient referral to treatment,** thus collapsing a current barrier in the HCV Cascade of Care.

We urge vigilance on the part of everyone concerned regarding possible unforeseen treatment side effects and long-term effects. Particularly we urge that **patients be carefully monitored for HBV and HCC** (especially those with prior history) **and the development of treatment-resistance**. Any of these should be made public and reported to medical practitioners and patient groups as quickly as possible.

13) Are there additional factors your organisation would like PhamaCare to consider during its review of this drug? (For example: does the drug meet any special patients' needs that have not been met by other drugs or treatments? Is the drug easier to use than other drugs; does the drug reduce visits to the hospital; does the drug reduce days off work or school; or are the drug's side effects acceptable or tolerable?).

FIRST OVER THE LINE PRICING: HepCBC recommends that BC PharmaCare not lose sight of the fact Epclusa® is simply one company's "recipe" using the universally-acclaimed molecule of sofosbuvir, the patent of which is now being litigated in many lawsuits world-wide. There are other pan-genotypic treatments which are well-advanced into the pipeline coming to us very soon, some of which use sofosbuvir, some of which don't. Just because Epclusa® is first over the line does not mean we should lose sight of those coming in second, third, and etc. such as upcoming products from AbbVie, Merck, Bristol-Myers Squibb and Janssen (and Gilead as well, with the possible addition of GS-9857 to the Epclusa® formulation).These upcoming combos could feasibly present equal or even superior efficacy at a significantly more competitive cost, thus collapsing the 'invisible' cost barriers within each step of the HCV Cascade of Care. CDEC has clearly recommended that drug plan costs of new DAAs should not exceed the costs of previous ones. However, **we encourage BC PharmaCare to go beyond that expectation, through its active engagement in current and upcoming collective price negotiations in the spirit of ensuring large numbers of guaranteed purchases in return for substantially lower prices.** This would be a win-win-win for patients, the province(s), and (presumably) the pharmaceutical companies as well.

F2+ RESTRICTIONS: As we have detailed in prior reviews, we remain concerned about the unusually high price of the new DAAs generally (sometimes referred to as 'orphan drug pricing' for an epidemic disease) which has resulted in ever more stringent treatment criteria in order to reduce the numbers of patients eligible to be covered by provincial/territorial drug plans (as well as private insurance plans in Canada and the USA). Being treated before a patient's liver has deteriorated significantly means a greater chance of treatment success, and the greater number of quality-adjusted life years (QALY's) the average patient will attain. It is essential to treat before patients reach a stage of liver disease where they can no longer safely be prescribed treatment.

HepCBC supports the need for urgently treating those most in danger of morbidity or mortality from hepatitis C (before they can no longer be safely treated). We accept that some patients with milder liver damage may have to play the waiting game for one or two years more. However, we strongly support treatment for all those who are HCV RNA positive, whatever their liver disease stage, after prioritised patients have been given the opportunity of a cure. In addition, we emphasize our opposition to the "F2 criteria" as an eligibility factor for treatment, while at the same time recognising that those who exceed this threshold are the most urgently in need of treatment.

Therefore, HepCBC requests acknowledgement from BC PharmaCare **that the reason it has not previously lifted treatment criteria requiring proof of significant liver damage** (often fibrosis level two or greater [F2+]) to qualify for HCV treatment coverage in our province is **the current high cost of HCV treatment, rather than any medical benefit to patients. Lifting these criteria — which now clearly ration a lifesaving medical cure —** would result in significant health benefits to British Columbians. Lifting this criteria is a policy recommended since May, 2016 by CDEC and CADTH at the federal level and, for several years has been strongly endorsed by the Canadian Association for the Study of the Liver, Canadian Association of Hepatology Nurses, Canadian Treatment Action Council, Action Hepatitis Canada, and the Canadian Liver Foundation. Prince Edward Island has fully lifted these restrictions and Quebec has developed a staggered plan for lifting them. We expect news any day of a plan from Correctional Services of Canada for lifting current restrictions in federal prisons. As such, HepCBC also requests that BC PharmaCare now boldly decides to **lift these criteria at this time *or sets a firm timeline for doing so*.**

EASY TREATMENT OPTION FOR PCPs: HepCBC has always advocated for diversity of HCV products and keeping them as much as possible on a 'stand-alone' basis, as a way to enable product "mixing and matching," to give physicians (and patients) as broad as possible a selection of choices and alternatives, and to foster price competition. Yet, on the other hand, we must **acknowledges that a "single product" approach, which products such as Epclusa® potentially offer, would simplify procurement, distribution, and adoption by primary care physicians**. While CADTH still recommends that treatment be initiated by physicians with experience in the management of CHC patients, HepCBC supports the concept that *all but the most problematic cases of hepatitis C will soon be* ***treatable at the level of general and family-care practitioners*** *in our province*, particularly important in providing treatment equity to residents of its rural and remote areas. We urge that the province **encourage this cost-saving, health-promoting, and equitable concept by consulting with all parties involved and supporting any professional development, administration, and infrastructure needs that would arise in its implementation**.

References:

NATAP Conference reports

SOF/Velpatasvir, +GS-9857 - Sofosbuvir/Velpatasvir Fixed-Dose Combination for the Treatment of HCV in Patients With Decompensated Liver Disease: the Phase 3 ASTRAL-4 Study At URL: http://www.natap.org/2016/APASL/APASL_28.htm [accessed on 28 April, 2016]

High Efficacy of Sofosbuvir/Velpatasvir Across 7 HCV Genotypes and 46 Subtypes: Pooled Data From the ASTRAL1, 2 and 3 Trials at URL: http://www.natap.org/2015/hepDART/hepDART_08.htm [accessed on 28 April, 2016]

EMA reviews direct-acting antivirals for hepatitis C: Review to investigate possible hepatitis B re-activation at URL: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Direct-acting_antivirals_for_hepatitis_C_20/Procedure_started/WC500203479.pdf [accessed on 16 April, 2016]

High rate of early cancer recurrence following direct-acting antiviral treatment for hep C virus at URL: http://www.eurekalert.org/pub_releases/2016-04/eaft-hro041316.php [accessed on 16 April, 2016]

Possible addition of GS-9857 to the Epclusa® formulation at URL: https://hepatitiscnewdrugs.blogspot.ca/2016/07/efficacy-of-sofosbuvir-velpatasvir-and.html [accessed on 21 September, 2016]

Quebec's staggered plan for lifting F2 treatment criteria at URL: http://www.capahc.com/en/hep-c-new-treatment-access-quebec/ [accessed on 21 September, 2016]

With thanks to Adam Cook and CTAC for an opportunity to analyse the data from the Astral trials at the webinar on 2 May, 2016