BC Pharmacare HepCBC Submission regarding Bristol Myers Squibb's asunaprevir (Sunvepra™)

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.

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, 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.

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. Those with undiagnosed hepatitis C are unaware that lifestyle changes 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 progressively debilitating symptoms plus there is the concern about 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 Sunvepra] 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 got 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 translation 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 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

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 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, and then about five years ago (2011-2013), the dual combination of peg-interferon plus the addition of a 1st generation protease inhibitor (PI) - either boceprevir or telaprevir) or occasionally with a 2nd generation PI, simeprevir. Boceprevir and telaprevir have been phased out as far superior drugs are now available, and peg-interferon 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.

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. In February this year Health Canada reported a possible link between simeprevir and liver function impairment and recommends that patients with moderate to severe liver damage should not use simeprevir.

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. The terrible side effects of Peg-INF, boceprevir, and telaprevir have given hepatitis C treatment a bad reputation. However, we are learning this is no longer the case with the new generation of (mainly) interferon-free DAA regimes, such as Sovaldi™, Harvoni™, Holkira Pak™ and now, there is also the possibility of Genotypes 1a, 1b, 3, and 4 being treated with Zepatier™ (elbasvir/grazoprevir) and Genotype 1 being treated with Sunvepra™ (asunaprevir) in combination with Daklinza ™ (daclatasvir) together with interferon/ribavirin in some cases.

Hepatitis C patients, especially those within our group, tend to be fairly knowledgeable and well-informed about their condition as well as 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. An increasing number of our group has had access to interferon-free treatments,

either in the context of a clinical trial or through new third generation DAA treatments (Sovaldi™, Harvoni™, or Holkira Pak™) now covered by BC PharmaCare. We are starting to hear many more success stories as people are treated with the new, far easier to tolerate, DAAs. We publish the rapidly-growing list of Canadians who have celebrated "SVR 12" on our "HepCBC Honour Roll" every month.

Over the decades there have been many treatment failures, particularly on dual therapy (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. In addition, peg-INF and ribavirin produce difficult side effects in most patients (e.g. influenza symptoms, anaemia sometimes leading to blood transfusions or even 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 concerting is the fact that the effects of peg-INF 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 (usually Harvoni™ or Holkira Pak™) report far fewer side effects. To date, we have not heard of long-lasting consequences like those experienced following treatment with interferon, although we have noted the recently-announced investigation by the European Medicines Agancy (EMA) into HBV reactivation following DAA treatment, plus we have also noted that recent research has identified a possible link between DAA treatment and resurgence of HCC, and between DAA treatment of cirrhotics and rapid liver decompensation, as well as other serious adverse events (J.H. Hoofnagle, EASL Journal of Hepatology 2016, vol. 64).

Here is what two of our patients have to say about the treatments they had previously tried before being offered an interferon-free combination of Sunvepra™ and Daklinza™:

Patient 1:

I took interferon 4 times: once, alone; once with ribavirin; once in a low-dose maintenance trial; once as Pegasys/RBV. I blame my eye problems on the interferon (cataracts, retinal tears, vitreous detachments…) I did not respond to any of these treatments, other than to keep the infection from doing more harm, and slowing down the progress of the fibrosis.

And Patient 2 writes:

I almost died during the first time I went through treatment (unsuccessful) with interferon and ribavirin (INF/RIBA); I was pulled off after 42 weeks. The INF/RIBA treatment left me with permanent damage to my thyroid gland, which hasn't improved at all since I got cured.

Three days after ending the INF/RIBA treatment, after having been flat on my back and unable to eat or even complete a sentence, with my organs shutting down, I was able to speak coherently and slowly walk up a small hill overlooking the city of Victoria with a friend, both of us completely amazed. I swore I'd never go on treatment again, and just live my life out as best I could, though I knew it wouldn't be long as I had rapidly progressing cirrhosis. That is, until one day in 2011 when a research nurse phoned, asking if I wanted to go onto a clinical trial with daclatasvir and asunaprevir. They needed people of my

age and clinical history with genotype 1B. So I fit their criteria! When I asked their opinion, all my 3 grown kids told me I'd be nuts to say no. The rest is history.

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

We are fortunate that two members of our group were treated as part of clinical trials with the combination of Sunvepra™ and Daklinza™ and so both are able to provide first hand evidence of their experience. Both patients were cured of their hepatitis C. They had this to say:

Patient 1 comments:

I took Sunvepra™ with Daklinza™ on a clinical trial. I responded. I am cured. I had no side effects. I can't express my gratitude enough!

Patient 2 remarks that:

I tried Sunvepra™ 4 years ago in a clinical trial, combined with Daklinza™, once a day. I took this medicine for 24 weeks. There were no side-effects whatsoever, and it worked. Plus, I am living proof that cirrhosis is REVERSIBLE if caught in time! Just before taking this combo, my Fibroscan score was 49.6 kPa (advanced cirrhosis). I've had several Fibroscans which documented the fairly rapid repair of my liver over the last 3 years. My last Fibroscan was 8 kPa (Stage 3 fibrosis - no more cirrhosis!). I feel great and my friends all say I look a lot healthier, too! If I weren't already retirement age, I'd consider going back to work again, as I feel like I've gotten my old friend - my brain - back! I also have started making plans to live to 100; sorry kids, you're not getting rid of me so soon!! I make the most of every wonderful day which is a bonus, a gift. I volunteer almost full time now for a hepatitis C organization.

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.)

We can answer Q12 using the words of our two patients who have both been cured after completing treatment using the drug under review:

Patient 1:

Being virus-free lets me hug my children and grandchildren with more confidence. I am widowed, and have a new boyfriend with whom I can enjoy life thanks to being virus-free. I don't have to worry about infecting others. I don't have to worry (hopefully) about liver cancer. I don't have to plan for a liver transplant. (I was infected in 1970). I am able to pursue my hobbies with a clearer mind than before.

And Patient 2 says:

To be frank, I'm not sure if Sunvepra™ is any better than the several other hepatitis C drugs, though I hear it has shown great promise when combined with other drugs for patients with special treatment needs. To me, the larger benefit of having a variety of hepatitis C drugs available is that it should encourage competition among companies which should, theoretically, result in lower prices over time.

OUR RECOMMENDATION:

HepCBC recommends the inclusion of Sunvepra™ in the BC PharamCare formulary. The data from the Hallmark trials supports the fact that it is an effective agent against hepatitis C for those with genotypes 1 and 4. In addition, because its action against the virus is different from other DAAs (see reference to the fixhepC website below), HepCBC believes it is important for clinicians to be able to prescribe Sunvepra™ as part of a treatment regime. As we point out in the next section, approval of as many effective and safe DAAs as possible is critical in efforts to eliminate hepatitis C.

Being free from the threat of complications arising from hepatitis C (cirrhosis, liver failure, liver cancer) and being free from the debilitating symptoms this disease causes will improve the quality of life. Sunvepra™ should be added to the list of effective treatments BC PhamaCare will be able to offer patients.

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?).

The experience of our two patients demonstrates that Sunvepra™ as part of an interferon free combination seems easy and straightforward to take. We cannot comment on how it would compare if it were combined with interferon and ribavirin (as it is possible to do) as we do not have anyone within our group who has taken it with these latter two drugs.

Patient 1 writes:

For me, the drug was simple to take. I had no problems or side effects. Honestly? I didn't need supervision or follow up, but it was nice to have support of the nurse and nice to have the feedback as to how I was doing.

Patient 2 reiterates these points by writing:

I think most people taking this drug would be able to carry on with normal activities; in fact, as the treatment goes along, they might even be able to do their normal activities with improved performance.

Approval is therefore recommended by HepCBC (although with the caveats we outline below). While treatments for hepatitis C with the new DAAs require close monitoring, side effects are minimal compared with older treatments. Patients undergoing treatment are far more likely to be able to continue work, study or go about their daily routine.

As HepCBC has written elsewhere and repeatedly, it is important that as many DAAs as possible are approved once they have been demonstrated to be both effective and safe in clinical trials. Approval of multiple DAAs will:

- Increase price competitiveness. There is near universal agreement among healthcare providers, both in Canada and worldwide, that the price of these medications remains unacceptably high, serving nobody's interests except the pharmaceutical companies.

- Enable medical professionals to become more proficient in prescribing DAAs more widely, increasing knowledge about both effectiveness and side effects as they relate to “real world” populations (in addition to those carefully selected for clinical trials).
- Produce more "real world" data allowing medical professionals to become experienced at “mixing and matching” DAAs to tailor treatments according to individual patient characteristics.
- Increase knowledge about side effects. In an “ideal world” any HCV drug regime would be completely free of side effects. However, this is never the case. While it is necessary to restrict access and to choose trial participants carefully for safety reasons, once a drug is approved and used more widely, additional concerns (contraindications, side effects) may come to light. All the approved third generation DAAs are highly effective, but their contraindications and side effects vary. We have to be prepared for additional side effects to surface as more people are treated. Both 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, a ‘noble’ role, but one we do not relish.

It should be noted that we would like to add the following caveats to our recommendation:

- HepCBC has noted that Sunvepra™ received a Notice of Compliance from Health Canada in March 2016 after a previous Notice of Non-Compliance had been issued in June 2015 following concerns over genotoxic impurity. These concerns have been satisfactorily addressed. However, we recommend close monitoring for those patients taking Sunvepra™ as part of a hepatitis C treatment regime (see additional comments we make below concerning AST/ALT levels when taking this treatment).HepCBC has noted that with some of the new DAAs, there is the possibility of serious liver injury in patients with advanced liver disease. If the Sunvepra™ under review is approved, we support stringent monitoring, reporting and evaluation of side effects until such time as it can be established that treatment with Sunvepra™ safe for the most vulnerable hepatitis C patients in Canada.For all patients who are prescribed Sunvepra™, there should be close monitoring for AST/ALT increases (see Health Canada Basis of Decision and BMS Product Monograph).For patients with G1b, the interferon free combination of Sunvepra™ + Daklinza™ is an excellent treatment. For those with G1a or G4, Peg-Inf + ribavirin must be taken in a treatment regime lasting 24 weeks. While the Quad combination is effective, clinicians need to weigh its benefits against those of other effective drug combinations for HCV (with or without Peg-INF + RBV) that may be equally effective, and of shorter duration.If approved, clinicians should ensure they are up-to-date with new guidelines as they become available in relation to treating HBV co-infected individuals with the new DAAs and in relation to data on HCC resurgence.

Subject to the points in the paragraph immediately above, HepCBC recommends approval of Sunvepra™. As we have detailed in prior reviews, we remain concerned about the exorbitant price of the new DAAs generally. Our concern is that these prices will result in ever more stringent treatment criteria in order to reduce the numbers of patients eligible to be covered by provincial/territorial drug plans. 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. Successful treatment puts a stop to HCV-related liver damage and in most cases results in some degree of reversal of liver damage, preventing other hepatic and non-hepatic HCV complications.

However, it is essential to treat before patients reach a stage of liver disease where they can no longer safely be prescribed treatment, and the earlier the treatment, the greater its positive effects.

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.

A related point is that we believe provincial governments must work together, rather than negotiate separately, to achieve fairer pricing throughout Canada for the new DAAs. There needs to be a co-ordinated, Canada-wide effort to ensure that the drugs are priced reasonably so that they are accessible wherever a sufferer lives.

The following sources provided material and references for this patient input review:

BCPharamCare *Asunaprevir:: Drug Information* internet WWW page at URL: http://www2.gov.bc.ca/assets/gov/health/health-drug-coverage/pharmacare/asunaprevir-3382-info.pdf [accessed on May 27, 2016]

Bristol-Myers Squibb *Product Monograph including Patient Medication Information Sunvepra* internet WWW page at URL: http://www.bmscanada.ca/static/products/en/pm_pdf/SUNVEPRA_E_PM.PDF [accessed on May 27, 2016]

Fixhepc.com *Sunvepra (100mg Asunaprevir) A New Hepatitis C Drug for difficult-to-treat patients* internet WWW page at URL: http://fixhepc.com/blog/item/53-asunaprevir-sunvepra-hepatitis-c-drug.html [accessed on May 27, 2016]

Health Canada *Sunvepra: Summary Basis for Decision* internet WWW page at URL: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd-smd-2016-sunvepra-172617-eng.php [accessed on May 27, 2016]