HepCBC Hepatitis C Education & Prevention Society's Patient Group Submission to the Common Drug Review at CADTH re: combo of Sofosbuvir/Velpatasvir/Voxilaprevir, August 19, 2017

Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest		Sofosbuvir in combination with velpatasvir and voxilaprevir (Vosevi™) (SOF/VEL/VOX)
Name of the patient group		HepCBC Hepatitis C Education and Prevention Society
Name of the primary contact for this submission:		**REDACTED**
Position or title with patient group		HCV+ volunteer
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Permission is granted to post this submission		X Yes ☐ No

CADTH will post this patient input submission on its website if permission is granted. See CDR Update — Issue 99 for details.

1.1 Submitting Organization

Founded in 1996, HepCBC is a registered non-profit society run by and for people infected with, or affected by, hepatitis C. In 2017 we are adding hepatitis B to our mandate. Our mission is to provide education, prevention and support to those living with viral hepatitis. We have two small offices in Victoria, BC and downtown Vancouver, BC. Most of our staff are volunteers with lived experience (either past or present) with viral hepatitis. We also employ four contractors on part-time, short-term contracts. We run activities in many areas of the Lower Mainland and travel throughout the province doing outreach. Our representatives attend provincial, federal and international conferences and participate at health-related events. In addition, we provide support and information globally through our website. Other activities include: Online publication of a weekly bulletin (the *weekly.bull*), plus peer support, anti-stigma activities and prevention education to the general public, general hepatitis information, particularly to baby-boomer, aboriginal and immigrant communities and those living in rural/remote locations. We support and encourage HCV and HBV testing among at-risk groups, including those who no longer fall into this category but may have contracted viral hepatitis decades ago, most commonly through the medical system (whether in Canada or abroad), or through recreational drug use. We also work alongside other organizations, including local HIV/AIDS organizations to support those co-infected with viral hepatitis and HIV.

1.2 Conflict of Interest Declarations

a) We have the following declaration(s) of conflict of interest in respect of corporate members and joint working, sponsorship, or funding arrangements:

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, Lupin Pharmaceuticals, Gilead Sciences, Janssen Pharmaceuticals, Bristol-Myers Squibb, and AbbVie, plus support from Rx&D, the pharmaceutical umbrella organization.

b) We have the following declaration(s) of conflict of interest in respect of those playing a significant role in compiling this submission:

All three of the authors of this report have attended numerous educational conferences and meetings for which registration and travel expenses were funded by the pharmaceutical companies listed in (a).

Section 2 — Condition and Current Therapy Information

2.1 Information Gathering

(1) Data came from patient surveys which were advertised through our website, Facebook Page, and our weekly email bulletin. Note that with each new Direct-Acting Anti-viral (DAA) submission we have received fewer responses. We suspect patients are feeling overloaded with requests for such information from then and they no longer see a reason to keep telling us the same things.

(2) Data came from volunteers and staff who have actively staffed HCV+ phone and email support lines over the course of several years, and therefore have an in-depth knowledge of patient concerns and experiences.

(3) Two of the authors of this report are/have been patient-researchers who have been reading scholarly articles about HCV for many years (20+ in one case).

2.2 Impact of Condition on Patients

In the last several years HepCBC has completed over 16 hepatitis C drug submissions for both CADTH and BC PharmaCare, and has answered Questions 2.2, 2.3, and 2.4 as many times. While we do present some new patient impact information at this time, we refer those wishing more detailed answers to five of our previous CADTH DAA submissions from 2016/2017, below:

http://hepcbc.ca/wp-content/uploads/2017/06/20170623_glecaprevir_pibrentasvir_CADTH_redact.pdf

http://hepcbc.ca/wp-content/uploads/2016/04/20150310_asunaprevir_SUNPREVA_CADTH_redact.pdf

http://hepcbc.ca/wp-content/uploads/2016/04/20141221_ombitasvir_paritaprevir_ritonavir_dasabuvir_CADTH_redact.pdf

http://hepcbc.ca/wp-content/uploads/2016/04/20141008_ledipasvir_sofosbuvir_HARVONI_CADTH_redact.pdf

http://hepcbc.ca/wp-content/uploads/2016/04/20140826_HCV_GT1_TherapeuticReview_CADTH.pdf

The first response is from a GT1 female from Ontario, age 68, now post-transplant:
"Over the years, I experienced fatigue a great deal, but there was nothing else causing problems that I knew of. I thought the fatigue was due to everything that I was doing – teaching and being an organist as well as doing my job as a wife and mother. I looked around at many friends and wondered why they weren't as tired as I was. No matter what, I couldn't stay up as late or do as much without getting overly tired. I figured it was just me. (Eventually…)*, my doctor called me into his office to tell me that he had noticed my blood platelets were going down.* (He referred her to an internist who told her…) *that my spleen was enlarged and that my liver was hard.* (But for over two years, no one followed up on this)*…I was having trouble eating some food. Fish, especially, made me throw up, so I stopped eating fish. I started being very careful about what I ate when we went out, being careful to avoid things that I thought might make me ill…I continued doing the things I usually did, including administrative work at the local music festival, but still felt fatigued a great deal of the time. I began to notice some little things happening. I saw white spots on my tongue. My Dr. sent me to an ENT, as he was concerned it was cancer. He looked at my tongue on the first visit, and set up a second visit to do a biopsy. When I went the second time, he decided that he didn't know what it was, but he didn't think it was serious. (I found out later that this was a symptom of liver disease, as was the fatigue). This was 2½ years after my first specialist. I think another six months to a year went by before I plucked up the courage to ask my doctor if my gallbladder could be causing my symptoms. I knew that throwing up after eating certain foods could be caused by gallbladder trouble, and I knew I did have some stones. The only thing was, I didn't have the pain that I thought was associated with gallbladder trouble. My right side was tender, though I thought it was from sleeping on my right side all the time. Fortunately for me, my doctor didn't question anything, and instead, asked which surgeon I'd like to see…As I waited in (the surgeon's) examining room, I knew the doctor was looking at things on the computer. When he came in to see me, almost the first thing he said to me was, "Have you ever had hepatitis?" My answer was, "Not that I know of." Off I went for blood work (almost everything on the page had been checked off* including Hepatitis A, B & C. He also sent me for a liver MRI…(She was told…) *I had hepatitis C, and it had damaged my liver."*

The second response was from a GT1b female from British Columbia, age 69:

"I knew I had hepatitis C by 1992, but was advised by my doctor that the treatment (interferon and ribavirin) would be too harsh to justify it, given the lack of symptoms I had at that point. Over time, the main effect of hepatitis C on my body was on my brain. I had always been a very logical, methodical, intellectually-active person who loved to read, do research, write, and teach. However teaching became too stressful, so I developed my own home-based business but was eventually forced to close it down (retiring early) due to an inability to concentrate, or to remember what I had said or done. I would regularly fall asleep sitting at my desk during the day, then wake up in the same sitting position, hours later, confused and alone in a dark house. Hep C also slowly started limiting what I was able to digest, eventually forcing me to cut meat, nuts, milk, and cheese out of my diet. I finally sought treatment for the first time in 2007, once strange chemical smells started emanating from my body."

The third response was from a GT2b female from the USA, age 63:
"Hep C drastically affected my life. It took about 25-30 years for me to start showing intense symptoms. I believe it took that long because I was not a drinker. But when the symptoms started it came on strong. I had intense body pain and overwhelming fatigue. I kept going to my doctor trying to get help. They had no idea what was going on; at one point I was accused of drug seeking. After about 6 months, I was having trouble at work. I worked at a major grocery store and was required to work various shifts. I had trouble getting to work on time and (eventually) *was fired. The funny thing is, I was initially glad because I could stay in bed and sleep. But within 2 months I was unable to pay rent and lost my apartment. I tried to get unemployment* (compensation) *but couldn't because I was too sick and was unable to look or accept any job. Because the doctors still hadn't diagnosed me I had no proof of my illness. I ended up sleeping in my car. After about 8 months my brother paid for a motel room for me but he felt I was faking it. So he quit helping after a few months. I was in my car for another year and went to a homeless clinic to get pain medication and help. My pain all throughout my body was intense. They ran a bunch of tests and found out I had HepC. It took another 2 months before I was able to see a liver doctor. He confirmed it and told me there were medications that could cure me. But I wasn't sick enough."*

The final respondent is a 70 year old male, living in British Columbia, with GT3, who underwent a liver transplant at age 66. He has had three previous unsuccessful treatment attempts. He suffers from a lack of energy and stamina which forced retirement at age 59. He writes that he needs treatment "before his new liver is compromised." He speaks for many GT3 sufferers when he writes that:
"Having type 3 means there are limited options for treatment and [I] would welcome any new treatments."
and (particularly since he is a transplant recipient):
"We don't want to go through hell again with my new liver."
Like many other patients, this man was infected via blood transfusion (in 1957 at age 10). He also writes:
"Treatment for GT3, post transplant has been hard to come by. [I] Hope it will relieve fatigue and other side effects".

2.3 Patients' Experiences With Current Therapy

Several all-oral treatments for HCV have been approved, both federally and provincially. However, collectively, they do not work for all patients and some may be contraindicated depending on a patient's characteristics. In our opinion, we need as many of the new DAAs approved as possible in order to increase prescribing flexibility, according to individual patient characteristics. In addition, although far less frequently than used to be the case, a few patients still fail the newer treatments. Cure rates are

very high: 95+% generally speaking. But 95% is not 100%. The hard truth is: some patients still fail the newer treatments, despite the fact that those treatments are extremely effective. These patients need to have hope that there still remains an effective option for them to try.

Patients who are rather harder to cure should have options, preferably without having to use the now-infamous drugs, interferon or ribavirin, if possible. Having a selection of multiple DAAs available is particularly critical in combating antiviral-resistant varieties which inevitably develop and spread, particularly among the "incident" populations of IV and intranasal drug users and men who have sex with men. The long-term consequence of resistance to HCV medications remains unknown, and any way of preventing or slowing its development (and staying ahead in the development of new treatments) is going to be key to the global elimination of HCV.

While approval of multiple DAAs reduces the likelihood of treatment failure, especially as additional data becomes available and doctors become more knowledgeable as they gain "real world" experience as to what combinations to prescribe. Those with genotype 3, those with advanced liver disease, prior treatment failure or coinfection (either with HBV or HIV) are examples of some groups for whom at least one (and ideally more than one) effective treatment option is required.

Currently, the biggest barrier to treatment with the new DAA combinations is their high cost, which has led to both private and public insurers rationing HCV cures. (One of our respondents: *"I couldn't believe that I was expected to get close to death before I would be worthy enough to get cured."*) Moreover, as liver disease advances, the risks and subsequent costs to society are greatly increased, even following successful treatment (even following treatment, an elevated risk of liver cancer, hepatic encephalopathy, and other elements of end-stage-liver-disease remain, at least for several years following achievement of SVR). However, the treatment combination under review might enable costs savings because it can be utilized as a shorter first treatment in those who are DAA naïve and without cirrhosis. We are at last starting to see price reductions, and in parallel with these we have seen some provinces reducing (or even abandoning) treatment rationing by striking down "proof of F2 or greater [F2+] fibrosis" treatment criteria. However, in our opinion, treatment rates remain very low while prices of treatment remain very high, even though some of the newer treatment regimes (for example, AbbVie's combo of glecaprevir and pibrentasvir) are significantly cheaper than others.

2.4 Impact on Caregivers

As noted in previous reviews, patients and their caregivers have repeatedly expressed to us that they want treatment options with greatly improved efficacy than in previous interferon-based regimes. In addition, they look forward to treatments which are shorter and require far less support, both mental and physical, than was previously required. Of course, they want their family members to regain their ability to support their families, or at least not be a burden to them, as soon as possible.

One of our respondents says, "*"[My] wife is (my) caregiver. [It is] very hard on her to watch me go downhill and deal with numerous medical problems."*

Another says, *"All of this was terribly hard on my adult children who were very worried about me but had no idea how to help."*

Another says her husband, *"helped me get dressed and move around the house, made meals, did cleaning and laundry and everything else with very little complaint."*

Yet another says: *"My son would come by and help wash my hair and bring me food. I could have gone to his apt to clean up but he shared it with 4 other people and I was ashamed and didn't want him to be embarrassed…"*

Section 3 — Information about the Drug Being Reviewed

3.1 Information Gathering

The information was gathered in the same way as for previous submissions (section 2.1). HepCBC staff and volunteers carried out their own research from the data available and used this in combination with patient experience to formulate an informed opinion. We attended a webinar put on by staff of the Canadian Treatment Action Council (CTAC) about this combo. And while we are aware that CADTH has access to all published data, we have referred to some published information, in support of several of the points we make, particularly in the following sections.

3.2 What Are the Expectations for the New Drug, or What Experiences Have Patients Had With the New Drug?

a) *Based on no experience using the drug:*

We studied Phase 3 clinical trial data which provide support for including SOF/VEL/VOX in provincial formularies. The success rates across the POLARIS 1 and 4 studies (those across all genotypes who were retreated for 12 weeks with the new combination following previous DAA failure) were 97%. POLARIS 2 evaluated 8 weeks of treatment across all genotypes in those who were DAA naïve. Cure rates were 95%, whether or not patients had cirrhosis. POLARIS 3 saw cure rates of 96% after 8 weeks and also 12 weeks of treatment for G3 patients with cirrhosis. Cure is defined as being virus free 12 weeks after cessation of treatment.

The unique factors about SOF/VEL/VOX would seem that it aims to provide a safe, effective, pan-genotypic, rapid cure primarily for those who require retreatment after failing a newer DAA treatment. Moreover, the additional good news is that SOF/VEL/VOX appears to provide an effective, shorter treatment option (8 weeks) for some patients who are DAA naïve and not yet cirrhotic.

Approval of the combination will offer hope by providing an effective salvage treatment to those patients, whatever their genotype, with or without compensated cirrhosis, who have previously failed one of the newer treatments, including NS5A and non-NS5A failures. Even those with baseline resistance associated substitutions (RASs) had SVR rates of 94 – 100%. In addition, the combination is effective in curing DAA treatment naïve patients without cirrhosis, of all genotypes, in as little as 8 weeks. However, our analysis of the data from the trials, together with other emerging data from patients who have been treated with the new DAAs, requires us to note some issues that need to be carefully considered along with any approval.

All-oral regimes are generally easier to tolerate than those containing interferon. Nevertheless, there are some side effects with every HCV treatment, albeit that the side effects are much milder and less likely to interfere with a person's normal daily activities than those in interferon-based therapies. Data from the trials indicate not only high cure rates but relatively mild (and to be expected) side effects amongst patients on strong medication. The side effects cannot be compared in severity to those that used to be routinely seen in patients taking interferon-based

therapy. The side effects appear to be quite similar to those experienced by patients on other all-oral HCV DAA treatments: minor cases of headache, fatigue, diarrhea and nausea.

We note a small number of Serious Adverse Events (SAEs) but these were seemingly not related to the treatment medication. In POLARIS 3, there was one death approximately 11 weeks following treatment but this is reported as being due to raised blood pressure (there was a history) and was unrelated to the medication received on treatment. A further patient died two days after 12 weeks treatment but this from a heroin/fentanyl overdose and therefore unassociated with treatment.

Thus, we anticipate fewer adverse events and less disruption to daily activities. Theoretically, there should be a reduction in hospital visits compared with the older, 1st or 2nd generation treatments. However, and as always, we support continued close monitoring of all patients undergoing any kind of HCV treatment regime. Although 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. They also do not, due to their nature, capture long-term data and thus do not show any long-term effects which might show up over time.

Furthermore, we have noted the recent and ongoing investigations 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. We believe that all HCV patients, considering HCV treatment with DAAs on an all-oral regime (i.e., no interferon), should have their HBV status confirmed prior to starting treatment. In this way, steps can be taken (e.g. the inclusion of anti HBV therapy) to minimize the risk of a potentially fatal HBV flare. We note that SOF/VEL/VOX will be dispensed with a boxed warning regarding HBV reactivation and contraindications such as treatment with rifampin.

We also note that research has indicated a possible resurgence of liver cancer for a short period 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. HCC is a factor that must be considered carefully before a treatment regime is prescribed, at least until more data becomes available.

b) *Based on patients' experiences with the new drug as part of a clinical trial or through a manufacturer's compassionate supply:*
We do not have any patients within our group who have tried this combination.

Section 4 — Additional Information

The points we have made in Section 3.2 above support:

Approval of SOF/VEL/VOX (Vosevi™), as it is a very versatile and effective treatment with high cure rates across all genotypes, even among those who are traditionally more difficult to treat. Critically, it provides a retreatment option of 1 pill a day for those who have already failed a DAA treatment. We recommend:

- Close monitoring of all patients on HCV treatment is required, whatever the regime.

- That doctors and specialists should be mindful of contraindications and the importance of keeping abreast of emerging data reflecting "real world" use.
- That HBV status and HCC history (if applicable) of an HCV patient needs to factored in to a decision on whether to treat, choice of treatment, and the monitoring regime to be applied both during and after treatment.
- That emerging data (especially in relation to treatment of HCV in those at high risk of HCC) continues to make a case for treating HCV patients before their liver disease is advanced.
- That greater access to treatments such as this one be assured to all patients who would benefit from them - through the continued lowering of prices and lowering of barriers to universal access such as requirements to prove significant pre-treatment liver-damage (F2+)
- The combination should be as easy to administer and to use as all the other approved 3rd generation DAAs, as it forms a single pill.
- In the overwhelming majority of cases, being cured of HCV will clearly benefit a patient in terms of their overall health.

References:

European Commission Grants Marketing Authorization for Gilead's Vosevi™ (sofosbuvir/velpatasvir/voxilaprevir) for the Treatment of All Genotypes of Chronic Hepatitis C, via URL: http://www.businesswire.com/news/home/20170728005201/en/European-Commission-Grants-Marketing-Authorization-Gilead%E2%80%99s-Vosevi%C2%AE [accessed on 2017-07-28]

Canadian Treatment Action Council (www.CTAC.ca) RECENT CTAC PATIENT GROUP INPUT CONSULTATIONS: SOFOSBUVIR/VELPATASVIR/VOXILAPREVIR (SOF/VEL/VOX), via URL: https://www.youtube.com/watch?v=hm-yQCSUM1k [accessed on 2018-08-16]

U.S. Food and Drug Administration Approves Gilead's Vosevi™ (sofosbuvir/velpatasvir/voxilaprevir) for Re-Treatment of Adults with Chronic Hepatitis C Virus, via URL: http://www.gilead.com/news/press-releases/2017/7/us-food-and-drug-administration-approves-gileads-vosevi-sofosbuvirvelpatasvirvoxilaprevir-for-retreatment-of-adults-with-chronic-hepatitis-c-virus [accessed on 2017-07-28]

The Safety and Tolerability of SOF/VEL/VOX for 8 or 12 Weeks in >1000 Patients Treated in the POLARIS-1, POLARIS-2, POLARIS-3, and POLARIS-4 Studies: an Integrated Analysis, via URL: http://natap.org/2017/EASL/EASL_64.htm [accessed on 2017-07-28]

A Randomized, Phase 3 Trial of Sofosbuvir/Velpatasvir/Voxilaprevir for 8 Weeks and Sofosbuvir/Velpatasvir for 12 Weeks for Patients with Genotype 3 HCV Infection and Cirrhosis: The POLARIS-3 Study, via URL: http://www.natap.org/2016/AASLD/AASLD_34.htm [accessed on 2017-07-28]