HepCBC Hepatitis C Education & Prevention Society's Patient Group Submission to the Common Drug Review at CADTH re: combo of glecaprevir and pibrentasvir. June 18, 2017

Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest		glecaprevir in combination with pibrentasvir for chronic hepatitis C
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
Email		REDACTED
Telephone number(s)		REDACTED
Name of author (if different)		Cheryl Reitz and Shakuntala Soden
Patient group's contact information:	Email	info@hepcbc.ca
	Telephone	250-595-3892
	Address	#20 1139 Yates St. Victoria BC V8V 3N2
	Website	www.hepcbc.ca
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. Our mission is to provide education, prevention and support to those living with HCV. We have an office in Victoria and another in downtown Vancouver, BC. Most of our staff are volunteers with lived experience (either past or present) with hepatitis C. 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 testing among at-risk groups, including those who no longer fall into this category but may have contracted hepatitis C decades ago, either through the blood 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 (for example with hepatitis B and/or 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:

Both of the authors of this report have attended several 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) Both 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 15 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 four of our previous CADTH DAA submissions from 2014/2015, below:

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

In this section, we include four responses to our request for patient input: one from a GT1 patient, one from a GT2b patient and two from GT3 patients.

The GT3 patients had both undergone treatment several times unsuccessfully. They reiterate the need for effective options for more difficult to treat populations such as theirs. We at HepCBC welcome the opportunity that any effective treatment would offer for GT3 patients, as well as for those infected with other genotypes.

The first response is from a female, age 62 from British Columbia, infected with GT3a. She has been through treatment twice and relapsed each time. Her main symptom from hepatitis C is a lack of energy. She writes that:
"… although I'm self-employed, I have trouble keeping up with work. At times [I] have to leave and go rest it gets worse as time goes by. I'm afraid of not being able to work some day."
She also mentions:
"The aches and pains" and "Never getting enough sleep."
However, she is not currently on any of the new therapies because she doesn't have enough liver damage to qualify for provincial coverage.

The second 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".

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 fourth patient is 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."*

2.3 Patients' Experiences With Current Therapy

Several all-oral treatments for HCV have been approved, both federally and provincially. However, these are not suitable for all patients. 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. Although far less frequently, a few patients still fail the newer treatments. These patients need to have hope that one day their liver disease will be cured — and without having to use the now-infamous drug, interferon, 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. 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 still required. It is becoming more and more apparent that there is no "one size fits all" treatment, so approval of multiple DAAs which can be mixed and matched according to rapidly-changing research recommendations, is highly desirable.

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. Moreover, as liver disease advances, the risks and subsequent costs to society are greatly increased, even following successful treatment (we comment on these points in later sections of this report). The cost factor means that those with less liver damage also suffer: Though it has been shown that the earlier a person gets treated, the more likely the treatment is to be successful, and the more quality years of life will be attained, most such patients are not permitted to access treatment unless they have either very generous insurance plans or are independently wealthy. This is particularly frustrating for HCV patients, caregivers and doctors. The existence of multiple DAA cures for HCV is bound to encourage a more competitive pricing structure which should result in the lowering of restrictive treatment criteria and economic barriers, making these cures far more widely available. Thus, the hopes and dreams of scientists, patients, and caregivers that this scourge can be completely eradicated from the face of the earth are coming much closer to fulfillment with each new DAA such as this new combination.

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 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). Some of our members attended a presentation by AbbVie, but our organization followed up on the presentation by doing its own independent research on the combination. In addition, although 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:*

Approval of the combination will increase treatment options adding to the all-oral regimes available. However, while HepCBC supports approval of the combination, 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.

The combination has been shown in the range of trials (for example: Expedition, Magellan, Endurance) to be highly effective globally across the main 6 genotypes, including difficult-to-treat populations such as those who have GT3, those who have cirrhosis, or those who have previously failed treatment (including with the new DAAs). A further positive result is that the combination appears to be both effective and safe even for those with renal disease. SVR12 (Sustained Viral Response after 12 weeks following end of therapy, in other words "Cure") rates are excellent at almost 100% for some populations, including high rates for those with the problematic GT3 (98%+), and those with cirrhosis. Furthermore, HIV co-infection did not affect cure rates and, in the majority of people, HIV therapy did not have to be interrupted. We note that the combination consists of a protease Inhibitor (NS3/4A) plus an NS5A inhibitor. For the small percentage of patients who have previously failed 3rd generation DAA therapy, glecaprevir/pibrentasvir offers an excellent chance for success which is extremely encouraging. Treatment duration is for either 8, 12 or 16 weeks, according to patient characteristics: to anyone who has taken an interferon based therapy for 48 weeks with its terrible side effects, this would seem to be a fantastically short duration!

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. The main side effects seen with this combination are documented as: fatigue, headache, nausea and pruritus. We note a small percentage of Serious Adverse Events (SAEs) but are reassured by the trial data which evaluates these as being unrelated to the treatment medication. As ribavirin is not included, its problematic side effects need not be considered.

Therefore, 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 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 have input from one patient who was accepted into a clinical trial for this treatment combo. This patient is female, aged 63, Fibrosis F2 and had been infected for approximately 30 years with GT2b. The patient had previously been unable to avail herself of treatment with the new DAAs because her specialist concluded that she was not sick enough. This was in spite of numerous devastating physical and emotional side effects from the HCV virus including her inability to continue to work and the subsequent loss of her home. Her experience with the clinical trial:

"The first 3 months I was on a placebo but was given the actual drug in April of 2016. My viral load dropped to half after 2 weeks. At 6 weeks I wasn't registering any virus in my system. At 3 months at the end of treatment I was told it looked like I was cured but wasn't 'officially' cured until my final blood test in Jan 2017. The only side effects I had were in the beginning I felt nausea. I was given some pills that took it away. No bad effects. It is hard to know if some of what I was feeling were side effects or effects from being ill with Hep. After I was treated my energy level went from 30% of normal to 80% of normal. I was able to stay awake for 4 or 5 hours at a time and was able to walk to store and bathe, etc. It slowly got better and I was able to do so much more.

Even though I was feeling quite sick and depressed when I was told I couldn't get treated through my insurance, it brought out this anger and determination to get treated. I couldn't believe that I was expected to get close to death before I would be worthy enough to get cured… I was the new reality. I also refused to suffer in silence. A few people I know were afraid to tell people they had Hep C. I ignored the stigma. I believe that allowing access to this drug will go a long way to getting rid of Hep C in our lifetime. It hurts me to know that so many had to continue to suffer because of not having the money to buy the drug. I don't know what else to say. It saved my life. Thank you for allowing me to participate. I am available any time if you need anymore."

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. The main side effects seem to be minor cases of fatigue, nausea, headache and itching.

Section 4 — Additional Information

The points we have made in Section 3.2 above support:

- Approval of glecaprevir in combination with pibrentasvir, 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.
- 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.
- The combination should be as easy to administer and to use as all the other approved 3rd generation DAAs. We note this particular combination means 3 pills a day, but as no ribavirin needs be included, this should not pose problems for most people.
- In the overwhelming majority of cases, being cured of HCV will clearly benefit a patient in terms of their overall health.

References:

U.S. FDA Grants Priority Review to AbbVie for its Investigational Regimen of Glecaprevir/Pibrentasvir (G/P) for the Treatment of Chronic Hepatitis C in All Major Genotypes (GT1-6) http://www.prnewswire.com/news-releases/us-fda-grants-priority-review-to-abbvie-for-its-investigational-regimen-of-glecaprevirpibrentasvir-gp-for-the-treatment-of-chronic-hepatitis-c-in-all-major-genotypes-gt1-6-300401029.html [accessed on 2017-06-17]

Pharmacokinetics and Safety of Glecaprevir/Pibrentasvir in Adults With Chronic Genotype 1-6 Hepatitis C Virus Infection and Compensated Cirrhosis: An Integrated Analysis http://www.natap.org/2017/EASL/EASL_10.htm [accessed on 2017-06-17]

Health Canada Grants Priority Review to AbbVie's Investigational Regimen of Glecaprevir/Pibrentasvir (G/P) for the Treatment of Chronic Hepatitis C in All Major Genotypes (GT1-6) http://www.newswire.ca/news-releases/health-canada-grants-priority-review-to-abbvies-investigational-regimen-of-glecaprevirpibrentasvir-gp-for-the-treatment-of-chronic-hepatitis-c-in-all-major-genotypes-gt1-6-612397593.html [accessed on 2017-05-19]

Hepatitis C Treatment Information Project: Glecaprevir/Pibrentasvir Granted Priority Review http://www.hepctip.ca/drug-pipeline-2/glecaprevir-pibrentasvir-granted-review/ [accessed on 2017-05-19]

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 2017-05-19]

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 2017-05-19]