Common Drug Review
Patient Group Input Submissions

sofosbuvir / velpatasvir (Epclusa) for hepatitis C, chronic

Patient group input submissions were received from the following patient groups. Those with permission to post are included in this document.
Canadian Liver Foundation — permission granted to post.
Canadian Treatment Action Council — permission granted to post.
Gastrointestinal Society — permission granted to post.
HepCBC Hepatitis C Education and Prevention Society — permission granted to post.
Pacific Hepatitis C Network — permission granted to post.

CADTH received patient group input for this review on or before May 12, 2016

The views expressed in each submission are those of the submitting organization or individual; not necessarily the views of CADTH or of other organizations.

While CADTH formats the patient input submissions for posting, it does not edit the content of the submissions.

CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no personal information is included in the submission. The name of the submitting patient group and all conflict of interest information are included in the posted patient group submission; however, the name of the author, including the name of an individual patient or caregiver submitting the patient input, are not posted.

Canadian Liver Foundation

Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest		Sofosbuvir/velpatasvir for chronic hepatitis C
Name of the patient group		Canadian Liver Foundation
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1.1 Submitting Organization

When it was founded in 1969, the Canadian Liver Foundation (CLF) was the first organization in the world dedicated to supporting education and research into all forms of liver disease. Today, the CLF continues to be the only national organization committed to reducing the incidence and impact for Canadians of all ages living with or at risk of liver disease. The CLF is the sole lay organization in Canada directing funds specifically for liver disease research and has invested more than $23 million in the scientific search for causes, preventative measures and potential treatments for liver disease, including viral hepatitis. As the largest community organization dedicated to liver disease, the CLF reaches over 250,000 Canadians through our public and professional education programs, patient support programs and other fundraising and outreach efforts. Over the past 45+ years, the CLF has invested more than $50 million in health education and prevention programs.

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:

In the past, the Canadian Liver Foundation has received unrestricted educational grants and/or has worked on joint initiatives with AbbVie Corporation, Astellas Pharma Canada Inc., Boehringer Ingelheim (Canada) Inc., Gilead Sciences Canada Inc., Janssen Inc., Merck Canada Inc., Novartis Pharmaceuticals Canada Inc. and Hoffmann-La Roche Limited.

Section 2 — Condition and Current Therapy Information

2.1 Information Gathering

To gather a broad range of input for numerous hepatitis C-related CADTH submissions, the CLF has repeatedly invited patients, caregivers and health care professionals from across Canada to fill out online surveys modelled on the CADTH questionnaire. The more than 400 responses to these various

surveys have been used in compiling the feedback for this submission. Quotes from survey respondents are included in italics in various sections of this submission.

2.1 Impact of Condition on Patients

Please note: *As the CLF has completed multiple CADTH submissions over the last several years for different hepatitis C therapies, we have repeated some content below that was included in previous submissions.*

The physical, mental and emotional toll that hepatitis C can take on individuals is similar across all genotypes. The majority of people living with chronic hepatitis C in Canada are adults within the 1945-1975 birth cohort who may have contracted hepatitis C either here or before coming to Canada and lived with hepatitis C for decades without any obvious symptoms. Regardless of whether they have recently been diagnosed or have been aware of their diagnosis for several years, a large number are now developing advanced liver disease and without treatment will progress to liver failure, liver cancer or need liver transplants.

"I have lived with hepatitis C for approximately 40 years. Symptoms such as insomnia, tiredness, itchiness, poor circulation, constipation and fear of accidently infecting someone else makes day to day life difficult. I am also concerned that delaying treatment is causing more liver damage." – hepatitis C patient

Individuals living with hepatitis C are often reluctant to talk about their disease for fear of the judgement of those closest to them. The stigma associated with hepatitis C can lead to misperceptions and fear amongst family, friends and co-workers and often personal relationships deteriorate or disappear completely. Without these support systems in place, individuals can spiral down into anger, depression and isolation.

"…whenever I have told people about my condition it was always met with criticism, fear and rejection. People seem to "know all about it" when, in fact they do not." - hepatitis C patient

"*I found out four years ago I had Hep C. It has not affected my ability to work, but it is always a huge concern for me. I have no idea when I contracted Hep C; it could have been thirty years ago, it could have been 5 years. Hep C has affected my relationship in a huge way. My spouse was diagnosed at the same time I was and he passed away Jan. 15/14 due to liver cancer caused by Hep C. Financially I am not able to afford any type of treatment for Hep C as I have no coverage whatsoever.." – hepatitis C patient*

Psychological and emotional stress only adds to the physical strain which comes as individuals progress to more advanced disease. While some may be able to manage the associated conditions triggered by hepatitis C, others find their lives unbearable due to debilitating symptoms which impact their ability to support themselves or even function on a daily basis. These symptoms can include nausea, headaches, sensitivities to light and food, memory loss, mood swings, itchy skin, abdominal pain, severe joint and muscle pain, portal hypertension, sleeplessness, slowed reflexes, psoriasis, peripheral neuropathy, osteopenia, diarrhea and muscle wasting.

"*I have had HEP C for 38.5 years. I have sensitivities to dairy, wheat, tomatoes, and sugar. Food becomes an issue a big issue for me. I also have low platelets, so I tend to get nosebleeds, bruise easily and have to be careful not to cut myself or injure myself in any way. I have lost interest in gardening because I just don't have the energy for that any more. I do not always sleep well at night; I have to be careful that I*

don't eat wrong foods as they keep me up as well. I have to be careful not to get colds because my immune system is low. I also get itchy because of bile in the blood and although I take a medication for it, the itch will keep me awake at night especially. I get very frustrated with living like this. It would be wonderful to find out what it is to feel normal." – hepatitis C patient

Not surprisingly, this litany of symptoms which can differ from individual to individual often means patients who once had full or part-time employment or even their own businesses must leave their jobs and rely on government support programs.

"Since late 1980 I was always ill with flu symptoms, tiredness, nausea, sensitive to light and noise, depressed, aches and physical pains I had to quit my job and my relationship with my family went from up and down to critical." – hepatitis C patient

2.2 Patients' Experiences With Current Therapy

Please note: *As the CLF has completed multiple CADTH submissions over the last several years for different hepatitis C therapies, we have repeated some content below that was included in previous submissions.*

Treatment rates in Canada continue to be very low meaning that many patients have yet to have undergone treatment. Conversely, there are patients who were diagnosed with hepatitis C many years ago who have undergone treatment multiple times unsuccessfully. Over the past four years, treatment options for genotype 1 patients have improved exponentially with the most recent interferon-free additions – sofosbuvir/ledipasvir (Harvoni) and ombitasvir/paritaprevir/ritonavir + dasabuvur (Holkira Pak) offering patients a low pill burden, few side effects, shorter treatment length (12 weeks) and, above all, efficacy rates of 90% or higher. Patients who have taken these or other interferon-free regimens have a radically different treatment experience than with previous interferon-based regimens.

"The first time I underwent treatment it involved pegylated interferon and ribavirin. I was very ill with fatigue, nausea and lost a lot of hair. In the end the treatment was unsuccessful. The next time I only had to take 2 pills a day for 3 months and the only side effect I had was a slight headache. Today I'm cured!" – hepatitis C patient

"I was diagnosed with hepatitis C in 2009 and by 2012 I needed a liver transplant. After my transplant, I was treated with a new drug combination that didn't involve interferon. The only symptom I had was a sensitivity to the sun that lasted about two weeks. In September 2014, I received the wonderful news that I was cured." – hepatitis C patient

Patients with genotypes 2, 3, 4, 5 or 6 have had more limited treatment options as the direct-acting antiviral therapies noted above are only reimbursed for genotype 1 patients in most provinces.

2.3 Impact on Caregivers

Please note: *As the CLF has completed multiple CADTH submissions over the last several years for different hepatitis C therapies, we have repeated some content below that was included in previous submissions.*

The burden of care for patients with hepatitis C often falls to spouses, parents and adult children. The symptoms of hepatitis C and the side effects of interferon-based therapy can leave patients completely dependent and unable to contribute financially, physically, psychologically or emotionally to the

household or the relationship. Caregivers report having to endure their loved one's mood swings, dietary problems, lack of energy and concentration while shouldering the responsibility for managing doctor's appointments, drug regimens and all household responsibilities. Due to a patient's inability to work, caregivers often become the sole income earner which adds even more stress. As the patient's symptoms and behaviour become more difficult to manage, families and marriages can break apart due to stress, financial difficulties and social isolation.

"Never knowing when the end is near. The worry about me being infected. When he gets sick I need to be here. Driving to all the doctors' appointments. The cost that comes out of pocket that affects our budget. Being restricted to travel. Trying to have some kind of normal" -- caregiver for hepatitis C patient

"I am now the primary source of family income. I am also the primary person in the family who deals with all insurance companies, forms, follow ups re LTD. I am responsible for more of the daily household chores, etc., I am responsible for a lot more now. It is no more 50-50." -- caregiver for hepatitis C patient

"Both of us transitioned from work - he was unable to work and I became the full time caregiver. As he transitioned from disability to retirement (age 65), with no continuation of disability, the financial impact has been significant. The impact on our children is significant - fear of losing their father, assistance with care, and the unknown. With the symptoms of the disease, sleep is difficult, both for the patient and for the caregiver. As a result, fatigue is relentless and it is so important to find ways to get rest to be alert. Medication monitoring is significant, especially when patient has MHE (minimal hepatic encephalopathy) or worse. Thus, the health and socioeconomic impact on the family and caregiver, and of course the patient, is serious and significant - and relentless." -- caregiver for hepatitis C patient

Many caregivers have had to manage through multiple rounds of treatment that often resulted in failure. Interferon-based treatments came with severe side effects but treatment with direct-acting antivirals has not only improved the outcomes but also the treatment experience itself.

"Treatment was March - August 2014 (third attempt at cure). All side-effects were manageable and so much less than any other regimen, despite his F4 cirrhosis and increasing MELD and symptoms. Anemia, fatigue, rash, leg cramps, and bowel disturbance were some of the side-effects, with the latter likely a result of the disease, not the medication. With the dosing regime, it is easy to administer and tolerate. He took the regime with ribavirin in the Gilead trial, and as a result, itchy rash was a symptom. Compared to the other two treatments he endured - first was 2006/7 with Ribavirin/Interferon and the second in 2012 with Telaprevir/Interferon/Ribavirin, this treatment was very manageable. The first was very difficult, the second try almost led to his death - became very very ill" – caregiver for hepatitis C patient

When patients were undergoing hepatitis C treatment with interferon-based drug therapies, it was a complex process that came with many side effects which often required additional medication. With the education and counselling required regarding treatment and side effects, care was very labour intensive for nurses and physicians. The new direct-acting antivirals do not require the same amount hands-on care as they have minimal side effects. Unfortunately, seriously ill patients undergoing treatment often have additional health conditions such as chronic kidney disease which can complicate care or even prevent them from being treated.

Section 3 — Information about the Drug Being Reviewed

3.1 Information Gathering

As mentioned previously, the CLF compiled its submission using numerous past survey responses from patients, caregivers and health care professionals from across Canada. We consulted with physicians who had treated hepatitis C patients with sofosbuvir/velpatasvir to gather their feedback on their patients' experience with the therapy but were unable to obtain feedback from patients who had taken the drug combination.

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

Hepatitis C genotype 1 patients have been the beneficiaries of a wave of new interferon-free direct-acting antiviral treatment options which offer up to a 100% cure rate. These patients still face challenges in accessing these therapies due to reimbursement criteria and time delays in approval but there are many more patients who can finally look forward to a prospect of a cure than ever before. Only recently have more treatment options become available for patients with genotypes other than 1 but these are not yet widely available. Due to the diversity of genotypes as well as complicating health conditions (i.e. HIV, kidney disease, advanced cirrhosis), there has yet to have been one drug therapy that worked for all genotypes. Hepatitis C treatment has therefore had to become very customized and only those that meet the reimbursement criteria of provincial drug plans or private insurers can afford treatment.

Sofosbuvir/velpatasvir is the first therapy that offers a 99 per cent cure rate across all genotypes (1-6) with only mild side effects (headache, fatigue, nausea). Many patients taking this therapy as part of clinical trials were convinced that they were taking a placebo because they experienced almost no side effects.

"Excellent experience across the board. One pill a day – doesn't get much easier. Much, much, much easier than interferon-based therapy. Many asked if they were on placebo!" – physician treating hepatitis C patients

Due to its versatility, sofosbuvir/velpatasivr has the potential to significantly increase the number of patients who could be treated and cured. While genotype 1 patients already have two effective treatment options, a 'one pill fits all' 12 week therapy that would work for all genotypes could simplify treatment decisions for both physicians and patients. Ultimately, hepatitis C patients, regardless of genotype, are looking for a safe, effective, affordable and easy-to-take therapy that will cure their hepatitis C and allow them to reclaim their lives.

Section 4 — Additional Information

Since the first direct-acting antivirals came on the market, hepatitis C treatment has been steadily improving but at the same time becoming increasingly customized in order to address individual patient needs based on genotype and additional health considerations. The Canadian Association for the Study of the Liver (CASL) has published multiple versions of its Consensus Guidelines for Hepatitis C detailing recommendations for what therapies to use for each genotype. The advent of a pan-genotypic therapy like sofosbuvir/velpatasvir could help simplify hepatitis C treatment for both patients and the physicians treating them. It could make it easier for primary care physicians to take on the treatment of hepatitis C thus making treatment more widely available outside of specialized clinics and urban centres.

In the absence of widespread hepatitis C testing (age-based in addition to risk-based), many people with hepatitis C are not being diagnosed until an advanced stage of their disease. This means that many will have already developed cirrhosis, both compensated and decompensated, which can make treatment more challenging. According to study results, sofosbuvir/velpatasvir is effective for patients with cirrhosis thereby further increasing its value and utility as a therapy.

It appears that sofosbuvir/velpatasvir may be the 'one pill fits all' therapy that both patients and physicians have been waiting for. It has the potential to give all patients, regardless of genotype, the opportunity to be cured in 12 weeks taking just one pill per day. For this treatment to have maximum impact however, it must be available to all patients who need it. Access will be determined by cost and without reimbursement, few patients will be able to take advantage of this latest breakthrough. It is critical that patients and their physicians have access to the best possible treatment options regardless of geographic location, financial status, treatment status or disease severity. Physicians are the most equipped to decide what treatment option holds the greatest odds of a cure for their patients so there should be no restrictions on access.

We therefore call upon CDEC to recommend reimbursement for sofosbuvir/velpatasvir for all genotypes of hepatitis C.

Canadian Treatment Action Council

Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest		SOFOSBUVIR/VELPATASVIR (Gilead Sciences) for the treatment of chronic hepatitis C infection (HCV)
Name of the patient group		CTAC
Name of the primary contact for this submission:		[redacted]
Position or title with patient group		[redacted]
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Telephone number(s)		[redacted]
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	Address	555 Richmond St. W, Ste 612. Toronto, ON.
	Website	www.ctac.ca

1.1 Submitting Organization

The Canadian Treatment Action Council (CTAC) is Canada's national non-governmental organization addressing access to treatment, care and support for people living with HIV and hepatitis C. CTAC's organizational goals are to meaningfully engage community members, service providers, policymakers and other relevant stakeholders to identify, develop, and implement policy and program solutions. CTAC understands that treatment access should be considered in its holistic form, encompassing the range of treatment, care and support needs required to reach the most successful treatment experience possible for people living with HIV and/or viral hepatitis co-infection.

Full CTAC membership is reserved for: a) individual people living with HIV (including HCV co-infection); b) organizations, groups or projects with a substantial HIV mandate (including HCV co-infection). Associate CTAC membership is open to any individual, organization, group or project that supports CTAC's mandate and objectives.

1.2 Conflict of Interest Declarations

CTAC received unrestricted organizational and educational grants from the following organizations in the 2015-2016 fiscal year: Abbott/Abbvie, Gilead Sciences, Janssen, and ViiV Healthcare.

Section 2 — Condition and Current Therapy Information

2.1 Information Gathering

On Monday May 2nd, 2016, CTAC conducted a national consultation webinar providing an overview of the Common Drug Review (CDR) patient input process as well as key findings from SOFOSBUVIR/VELPATASVIR (hereafter referred to as SOF/VEL) clinical trials (specifically the ASTRAL series). These trials examined SOF/VEL in comparison to Sofosbuvir as well as the inclusion of Ribavirin (RBV) for some patient populations. The patient consultation was presented by Adam Cook, Policy Researcher at CTAC. CTAC membership, organizational partners, and interested stakeholders were

invited to participate. Principal investigators from the ASTRAL series of trials were alerted to our consultation and asked to inform trial participants that CTAC seeks patient input.

8 people attended the webinar. A link to the consultation webinar video and online feedback survey were provided to webinar attendees. The link to the video was then made available to all interested parties and stakeholders upon request. The accompanying survey was live from May 2nd until May 11th, 2016. CTAC has compiled data from the feedback survey. All respondents had viewed the webinar, save one respondent (a clinical trial participant) who provided feedback via phone, as access and availability issues prevented their participation in the webinar (no consistent computer/phone access at time of consultation).

6 respondents completed the survey in full. 3 identified as male, 2 identified as female, and one identified as Two-Spirited First Nations Female. 2 respondents were from British Columbia; 2 from Ontario; and 1 each from Alberta and Saskatchewan. The median age of respondents was 48. 1 respondent identified as HCV+, 2 as HCV-, 1 as HCV- following treatment, 1 unsure of their status, and 1 identifying as an HCV- caregiver. Only 1 respondent was experienced with SOF/VEL, having achieved SVR (sustained virologic response) after participation in the ASTRAL series of clinical trials for SOF/VEL. Some patients declared a treatment-history, experience, or knowledge of the medications SOFOSBUVIR (a component of SOF/VEL) and Ribavirin (RBV, a component of the SOF/VEL medication in some trial arms). Accordingly, testimonies regarding these medicines from CTAC's Patient Input responses to SOVALDI (sofosbuvir), HARVONI (sofosbuvir and ledipasvir) and DAKLINZA (daclatasvir, which is often paired with sofosbuvir) have been used to complement this report where appropriate.

2.2 Impact of Condition on Patients

Hepatitis C is a serious and life-threatening virus that can impair liver functions, lead to cirrhosis, and is considered the leading cause of hepatocelluar carcinoma. Most recent data from Health Canada suggests that as many as 300,000 Canadians are presently infected with HCV, with as many as 70% of those unaware of their infection and Health Canada data further suggests there are as many as 8,000 new cases annually.

A hearty and unique virus, HCV is transmitted through blood-to-blood contact. While approximately 20% of people infected will pass the virus naturally, approximately 80% will not and the presence of the virus will develop into a chronic HCV infection. Asymptomatic for much of its cycle, HCV infection slowly causes significant liver damage, contributing to fibrosis, cirrhosis, and even liver cancer. Past strategies for treatment suggested a wait-and-see approach to determine if the virus was passed naturally, or to confirm that liver damage progression (fibrosis) was fast and severe enough to demand treatment (metavir score > F2). New evidence, however, suggests that more than 60% of all HCV sufferers will sustain fibrosis and incur liver damage necessitating quick and effective treatment. Left untreated for long periods of time, chronic HCV can lead to decompensated liver cirrhosis or hepatocellular carcinoma, the leading causes of liver transplantation in Canada. Consider the impact of this strategy to special populations in Canada, as one caregiver respondent noted, "As an example, an individual I am working with had taken great strides to achieve stability in her life with the hopes of getting on hepatitis C treatment. She is in supportive housing, and had stopped her substance use. After visiting the hepatitis C clinic and being told she was not eligible because her liver was too healthy, she questioned why she had put all that effort into maintaining sobriety and began her substance use again, putting her housing at risk. She had all the pieces lined up, and would have been in a good spot to initiate treatment, however this news has sent her on a path that may indeed lead to liver damage, but also a more chaotic situation that would not be conducive to an easy treatment for her."

HCV's often-asymptomatic nature is considered an important variable in its prevalence and spread. Many people live unknowingly with this infection and quietly suffer significant damage. As one HCV sufferer responding to CTAC survey reported, "*I was unaware that I had hepatitis C until 2009, some 30 years after contracting it. It is my understanding that there are ongoing symptoms… but all would have been considered a normal part of my adult life as I was a teenager when I was infected.*" Most people seek diagnosis and treatment when experiencing symptoms of fibrosis, cirrhosis, or severe liver damage, but these symptoms are the result of the infection already being possibly decades old. The respondent continued, "*I was diagnosed with F3 liver damage, so it is reasonable to say that hepatitis C treatment saved my life.*" HCV sufferers do sometimes report impact of their infection or liver damage early, however. Many respondents echoed the remarks of one 52 year-old female from British Columbia, who said her symptoms included "Chronic fatigue, some short-term memory concerns." Both of these symptoms significantly impacted the sufferer's ability to maintain employment or social activities.

A significant number of people living with HIV infection are co-infected with HCV. Approximately 13,000 Canadians are co-infected with HIV and HCV. Extrapolating from existing Health Canada data, we can postulate that approximately 20% of all people living HIV would be infected with HCV, and approximately 5% of all people living with HCV would be infected with HIV. Not only do people living with co-infection suffer under increased stigma and differing treatment needs, both viruses exacerbate the progression of the other, and many of their respective medications impact one another. For example, patients using HIV protease inhibitor tipranavir-ritonavir must be careful of possible drug interactions with sofosbuvir-based HCV treatments.

While the Public Health Agency of Canada has suggested that a significant proportion of those infected by HCV are receiving treatment, IMS MIDAS market data publicly reports HCV treatment sales, which suggest that approximately only 10,000 of the suspected 250,000+ are currently being treated. While HCV treatments become more effective and more tolerable, the relative lack of sufferers being treated is a conspicuous and jarring discrepancy.

2.3 Patients' Experiences With Current Therapy

One respondent identified as HCV+ and one identified as having achieved SVR after treatment with SOF/VEL for 12 weeks. 1 respondent was unsure of their HCV status. Of these, 2 are considered to have treatment experience with Direct-Acting Antivirals (DAA), whether SOF/VEL or another DAA. 2 Respondents were also treatment experience with RBV or had provided care for someone undergoing treatment with RBV. Respondents indicated complicated treatment regimens dependant on genotype and clinical criteria were a continued barrier to access to treatments. Accordingly, there was some positive anticipation among respondents that SOF/VEL is considered pan-genotypic and can treat HCV genotypes 1-6.

Respondents continue to identify the most persistent treatment side effects of any HCV treatment as being, "fatigue Insomnia Constant (daily) headaches Weight loss Suppressed appetite Hair loss Some cognitive difficulties such as word recall Depression Irritability & easy to anger Short term memory loss Joint pain." Fortunately, the treatment landscape continues its robust and dynamic course and patient groups are extremely optimistic about the safety and efficacy of new DAAs while being very concerned about the public availability and accessibility of the same.

Several respondents suggested that clinical trials are looking to improve subsequent generations of DAAs over previous ones, but regretted that ribavirin, and occasionally interferon, were still being used or reviewed and used in newer treatments.

New treatments, such as those including SOFSOBUVIR, promise to shorten treatment duration, increase efficacy and tolerance. It is worth noting, however, that at present, even newer medications are prescribed with pegylated interferon and/or ribavirin depending on past treatment experience, liver damage, or response-guided therapy. The persistence of out-dated therapies is itself impactful, as one support worker commented, “For those who do get the treatment, dealing with the side-effects can be extremely difficult, in particular, the depression. The injections associated with the interferon can also be a triggering factor for many people as well as a source of anxiety, given that many individuals being treated for hepatitis C have a history of injection drug use.” This was echoed by many caregivers, who regularly noted the social impacts of HCV treatment, including “heavy pill burden, multiple side effects, dealing with needle phobia, or triggers with regard to past lifestyle.” Further, a respondent to the SOF/VEL consultation noted that their treatment history included past experience with pegylated interferon and RBV, and was quick to caution “I have cleared HCV with the earlier interferon/ribavirin combo and would not wish that treatment on anyone as it has had long term adverse effects on my health.”

As one caretaker respondent reported, “Living with someone who is taking interferon & ribavirin can be extremely challenging.” Another respondent, themselves treatment-experienced, noted the impact treatment had not only on their well-being, but their relationships, noting that “Interferon is a very taxing, difficult drug. We need to eliminate it as soon as possible… I suffered through virtually a whole year of treatment on the interferon regimen and it was brutal.”

There were respondents experienced with first generation *and* some experienced with newer and current-generation HCV therapies, and all respondents expressed a positive outlook regarding the trials our webinar discussed. Specifically in the reports of few serious adverse events, minimal drug drug interactions, and a comprehensive safety profile. Further, many respondents chose to contextualize this development as indicative of an industry-wide pharmaceutical response to the community call for more tolerable cures for HCV.

Even achieving SVR on a new DAA may come with unanticipated health outcomes and it is important that vigilance is maintained in monitoring HCV patients even after treatment has been completed. As one respondent noted “I’ve heard stories from people who have felt worst after taking DAAs and achieving SVR. This hopefully is a short term thing, but it makes me unsure.”

2.4 Impact on Caregivers

In addition to caregiver testimony provided in section 2.3, caregivers involved in HCV service and support continue to report the following as recurrent symptoms of the HCV virus as well as HCV treatment: fatigue, nausea, depression, anorexia/weight loss, and anxiety associated with side effects or the prospect of treatment failure. Respondents continue to note the large incidences of side effects associated with RBV in the ASTRAL trials.

Eligibility criteria for access to new DAAs is inconsistent between provinces and territories, and often calls for evidence of liver damage before treatment can be initiated. These requirements are frustrating for individuals, “especially those who are experiencing multiple barriers, to be told that they are not sick enough to start treatment.” This places immense burden on caregivers to help navigate a complex and dynamic treatment landscape as well as call upon them a quick and coherent uptake of changing treatment requisites and standards. As a service provider noted, both patients and caretakers can be frustrated by this, stating that patients were “not taken seriously until their health is seriously compromised.” One caretaker listed some of their more significant challenges as “being able to provide

them with the most up-dated information on treatment regimes, however, then not being able to provide them with the ability to access these newer agents. -keeping them engaged while they wait - helping them understand their degree of disease & inability to predict disease progression/changes." Attendees to the SOF/VEL survey noted that inconsistent access to the same medication across provinces was an obstacle in need of reform.

Monitoring the rapid development of medical science knowledge is extremely important in the daily work of the caretaker, but only complement the more traditional task of aiding patients' experience of stigma and social isolation, as one noted, "There are many challenges in supporting people with hepatitis C…social issues including stigma due to ignorance of transmission risks as well as assumptions made about individuals' lifestyles. This stigma often comes from doctors and other medical staff as well as support workers in community organisations, and can be an unexpected barrier to receiving service." Even these obstacles only serve to further exacerbate other existing challenges, such as staffing ("we don't have enough personnel to take care of these people,") or funding ("not being able to get funding for certain treatments is a challenge,").

Section 3 — Information about the Drug Being Reviewed

3.1 Information Gathering

The information in this section was gathered in the same manner as described in section 2.1.

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

Only one respondent was experienced with SOF/VEL. CTAC continues to struggle to find treatment-experienced patients for new medications and have adopted new strategies to correct this problem. CTAC regularly contacts principal investigators of clinical trials and attempts to expand our call for patient testimony over various social media platforms. CTAC would enthusiastically welcome CADTH input, insight, and assistance into a strategy for patient groups to manage this very important discrepancy in our Health Technology Assessment processes.

Several respondents expressed enthusiasm SOF/VEL ASTRAL trials looked at harder to treat patients, but noted that trial demographics continue to be unrepresentative of real world populations (for example, the majority of participants were middle-aged white males). Further, one respondent noted the important of a "cultural approach" not just in treatment of HCV in communities, but also in the design of random control trials. As our First Nations bear a disproportionate load of our national HCV burden, we must be better representative of their unique struggles in all clinical trials. As one respondent noted, many rural and indigenous communities seek to "cure with traditional meds" and seek cultural approaches to treatment "taught by Natives to Natives." If treating these populations is a serious priority, Canadian review bodies must be more rigorous in demanding such data from manufacturers and principal investigators.

2 respondents said that, were it appropriate to their status and treatment history, they would have taken, or considered taking, SOF/VEL. Some respondents were still unsure of the severity or impact of side effects with one respondent saying they would be unsure if they would take SOF/VEL, stating they were "not convinced about safety yet. Seems these drugs were pushed to market rather quickly." A SOF/VEL respondent acknowledged that SOF/VEL side effects seemed to be "less than PI or older treatments. Skin related, headaches, flu like symptoms, or those reported in clinical trials, and effects posted for SOF after it came to market." This note was echoed, as webinar attendees reiterated concern

for post-market surveillance and post-treatment monitoring of new DAAs and their maintained, long-term impact to health outcomes *after* achieving SVR.

Overall, respondents anticipated SOF/VEL would contribute to increased quality of life. One respondent noted "I imagine that it would affect my daily routine but I am unsure as to how much." This remark is representative of a larger consistent narrative observed among HCV stakeholders: perhaps new DAAs are nearing their *critical-efficacy*, and if the future holds pan-genomic medicines with only marginal differences in SVR efficacy, cost-effectiveness becomes an increasingly important and valued variable in Health Technology Assessment. As a SOF/VEL respondent explained, SOF/VEL does "offer a choice, but the price must be comparable to Harvoni, or I see no value in this product." Past respondents have expressed concern regarding the price of DAAs and how a new pan-genomic treatment would be priced, considering its increased efficacy and ability to treat more people. If new DAAs are priced problematically, what can Canadian patients anticipate in the pricing of a more effective, pan-genomic treatment?

Respondents were asked to evaluate the patient input consultation webinar in the corresponding survey. Over 90% of respondents reported that their knowledge of SOF/VEL was increased "somewhat" or "significantly." Additionally, attending the webinar was "significant" or "very significant" in making over 90% of respondents feel engaged in the HCV response in Canada.

Section 4 — Additional Information

CTAC continues to acknowledge and appreciate CDEC suggestions as to how to improve patient input submissions. CTAC also reiterates our appreciation for every opportunity to provide patient input and testimony to support CADTH activities.

Gastrointestinal Society

Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest	Sofosbuvir-Velpatasvir for chronic Hepatitis C infection
Name of patient group	GI (Gastrointestinal) Society
Name of primary contact for this submission:	[redacted]
Position or title with patient group	[redacted]
Email	[redacted]
Telephone number(s)	[redacted]
Patient group's contact information:	
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Address	231-3665 Kingsway, Vancouver, BC V5R 5W2
Website	www.badgut.org

1.1 Submitting Organization

Our mission: As the Canadian leader in providing trusted, evidence-based information on all areas of the gastrointestinal tract, the GI (Gastrointestinal) Society is committed to improving the lives of people with GI and liver conditions, supporting research, advocating for appropriate patient access to health care, and promoting gastrointestinal and liver health.

Canadian health care professionals request more than 550,000 of our BadGut® Basics patient information pamphlets each year, and tens of thousands of Canadians benefit from our important quarterly publication, the *Inside Tract® | Du coeur au ventre*[MC] newsletter.

Our free BadGut® Lectures from coast to coast cover various digestive conditions for patients, caregivers, and other interested individuals. We also have dynamic websites in English (www.badgut.org) and French (www.mauxdeventre.org). Organized on a number of topics, GI Society support group meetings offer a wealth of information for those newly diagnosed with a gastrointestinal or liver condition, as well as those who have lived with an illness for years.

Our highly trained staff and volunteers offer additional patient resources, including responding to information requests and participating in community initiatives. Staff and advisors work closely with health care professionals, other patient groups, and governments at all levels on behalf of GI patients. In addition, we occasionally hold continuing education events for pharmacists, nurses, dietitians, and physicians. The GI Society, along with its sister charity, the Canadian Society of Intestinal Research (CSIR – founded in 1976), has supported a number of significant clinical, basic, and epidemiological research projects in the field of gastroenterology/hepatology.

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:

The GI Society receives financial contributions from many pharmaceutical companies in addition to governments, foundations, and individuals in support of our independent charitable work for Canadians affected by GI/liver conditions. Supporters have no input into the editorial content of our resource material, which is approved by the GI Society's Medical Advisory Council (made up of GI/liver health experts only). Other pharmaceutical companies from whom we have received support of any kind, such as charitable donations or grants, sponsorships, subscriptions to the Inside Tract® newsletter, etc. in the last two years include AbbVie Corporation, Actavis, AstraZeneca Canada Inc., Innovative Medicines Canada, Ferring Inc., Gilead Sciences Canada Inc., GlaxoSmithKline Inc., Janssen Canada, Merck Canada Inc., Pfizer Canada Inc., Shire Canada Inc., and Takeda Canada Inc.

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

None. The GI Society has solely prepared this submission entirely independently of any outside groups or individuals.

Section 2 — Condition and Current Therapy Information

2.1 Information Gathering

This information was obtained primarily through contact (interviews, etc.) with patients affected by hepatitis C (HCV) and HCV nurse specialists, as well as the expertise of our health care professional council and advisors (gastroenterologists, hepatologists, pharmacists). We held a meting with Hepatitis C patients as recently as May 10, 2016.

2.2 Impact of Condition on Patients

HCV can affect patients in every facet of their lives, including professional and personal relationships, and in their ability to perform required duties at work and at home. It is one thing to care for one's self, but many with HCV are also caregivers of others.

HCV becomes chronic in approximately 75% of those infected. Most chronic carriers have few or no symptoms but some report fatigue (even extreme, disabling fatigue), general weakness, and vague discomfort in the area around the liver. In about 25%, chronic HCV can lead to cirrhosis of the liver and cirrhosis can lead to liver cancer. All these symptoms and potential outcomes take their day-to-day toll and can lead to death.

The biggest physical factor patients report having to manage is fatigue. What is worse, the fatigue can be unpredictable. Some have to ask themselves each morning, "Will I have enough energy to do the things I need to do today?" If HCV symptoms disrupted their sleep the night before, as it often does for patients with more severe disease, then the answer will be "No."

Similarly, the disease can affect cognitive functions. Try to imagine getting through your day when memory and focus are illusive because your body has to work so hard to clear toxins via a liver that is functioning at far less than capacity.

The GI Society represents patients with a variety of gastrointestinal and liver conditions, almost all of which are highly stigmatized. It is not easy to talk about an infection with hepatitis C. Patients can begin to define their lives by their disease while hiding it from others. They might suffer from depression, anxiety, isolation, and other mental health consequences of a hepatitis C infection.

A cure means freedom from days filled with debilitating fatigue and from lives dominated by stigma-centred fear. Healthy people with optimism about their lives and physical health can have a positive impact on reducing the public health care burden. Additionally, as those with hepatitis C carry on with the virus ravaging their bodies, they are more likely to spread the disease to others. By eradicating the virus from infected individuals, we can prevent its spread.

2.3 Patients' Experiences With Current Therapy

The former Standard Therapy for HCV is long and grueling and can last for as long as forty-eight very difficult weeks, during which patients can experience extreme fatigue, depression, and other symptoms. This rarely cured Hepatitis C.

Triple therapy medications, such as boceprevir and telaprevir, combined with ribavirin are an improvement over dual therapy, but they come with additional side-effects and require a patient to adhere to a regimen of many pills (as many as 12) taken throughout the day, often with specific food requirements. In contrast, patients undergoing treatment with Direct Acting Antivirals (DAAs) such as grazoprevir-elbasvir combination, sofosbuvir-ledipasvir (Harvoni®), and sofosbuvir (Sovaldi®) take a single tablet each day. Other DAA's like ombitasvir-paritaprevir-ritonavir-dasabuvir (Holkira™ PAK) and Technivie™ require patients to take multiple tablets daily and at different times of the day.

In many cases, the benefit of a likely cure from a life-long sentence with HCV may very well be worth the risks of serious complications or a temporary increase in uncomfortable symptoms. These patients need access to medications that can reduce their suffering and maximize their chance for a cure by taking a therapy that is effective in a much faster timeframe.

Furthermore, patients who have failed Standard Therapy and triple therapy, or who are HIV co-infected, have kidney problems, or who have other HCV genotypes need further options. Physicians need options when deciding which curative treatment to use for each unique patient. The sofosbuvir-velpatasvir combination offers a new, effective option to those patients not already successfully treated.

Hepatitis C treatment often means having to take time off work and major childcare or other caregiver duties to deal with side-effects, putting an extra societal burden on other family members. A short treatment time with fewer side effects means less hardship for the patient and all family members and caregivers.

More than anything, patients have told us that improved cure rates, decreased adverse effects, simpler treatment regimens, and shortened treatment times are of paramount importance to them on an emotional and physical level. As a chronic disease, treatment for hepatitis C is complicated by how it requires the patient to be fully committed to their treatment. For them to be committed, they must have hope for a good chance at cure, they must have tolerable physical and emotional adverse effects, and they must have a treatment regimen that they can incorporate into their lives.

2.4 Impact on Caregivers

Once patients begin therapy for hepatitis C, they require support from virtually every person in their social circle to succeed. One patient we spoke with, who endured 48 difficult months of dual-therapy treatment side-effects, explained how his crucial support circle included everyone from his nurse support specialist (of which there are far too few in this country), family, friends, co-workers, and so on. He credits them with making it possible for him to endure the side-effects, which included anemia,

anxiety and depression, and extreme sensitivity (physical and emotional). His nurse specialist described treatment as “grueling hard work for everyone involved”.

Older hepatitis C therapy means having to take time off work and major childcare or other caregiver duties to deal with side-effects, putting an extra societal burden on other family members. A shorter treatment time with fewer side effects will mean less hardship for the patient and all family members and caregivers.

Section 3 — Information about the Drug Being Reviewed

3.1 Information Gathering

This information was obtained primarily through contact (interviews, etc.) with patients affected by hepatitis C, hepatitis C nurse specialists, and the expertise of our health care professional council and advisors (gastroenterologists, hepatologists, pharmacists).

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

a) Based on no experience using the drug:

Patients would like to receive treatment as soon as possible and most patients also express a willingness to endure some risks and side-effects, but minimizing these is best for everyone. Decreasing treatment time is a priority for patients and health care providers, mainly due to the burden of side effects during treatment. Sofosbuvir-velpatasvir is just one pill a day and patients take it for as few as 12 weeks, further minimizing potential side-effects. In addition, the sooner a person is effectively treated (i.e., **cured**), the less chance they have of inadvertently infecting someone else.

These factors enable HCV-infected patients them to adhere to treatment and get back to a normal live as soon as possible.

Sofosbuvir-velpatasvir offers hope to patients who are infected to any degree across HCV genotypes 1-6, as well as those who failed previous treatments and those with genes that have been associated with a poor response to interferon therapy.

Low socioeconomic status is a risk factor for HCV, which means it is one of the demographics that is most susceptible to becoming infected with HCV. It is also very unlikely to be able to afford this new treatment without public plan coverage. While patients languish with this disease, their chances of recovery are diminished, not just physical recovery, but in the sense of getting over the disease and moving forward with their lives and participating as valuable citizens in the community. This is a clear matter of social equity.

We realize that this new treatment will likely be expensive, as are the ones approved before it but, in the long-term, unhealthy people are more of a burden on the health care and social systems than are healthy people. Particularly with patients who have severe forms of the disease (e.g., cirrhosis, liver cancer), the long-term effect of being denied appropriate treatment will likely be far costlier, in the forms of liver transplants or other on-going, expensive medical treatments and interventions (both medical and social).

The health technology assessment around sofosbuvir-velpatasvir should weigh the new benefit of a cure that works well across the 6 HCV genotypes as a paramount goal of treatment for the patients who need it. This is a remarkable opportunity to eradicate the virus from many high-risk individuals in Canada as well as from the population at large and to prevent further spread of a malevolent infectious disease that has no vaccine.

Improved cures for HCV like sofosbuvir-velpatasvir will help decrease the spread of the disease, leading to less stigma and better education around HCV. Ultimately, this will lessen the financial healthcare burden, which of course is also a taxpayer's burden. We are doing our part to educate on hepatitis C with our video. Please take time to view the video as part of this patient input submission.

It makes sense to us, and to the patients who we represent, that when a medication is available that offers a cure, the person with the disease should have reasonable access. Both those who have not responded to previous treatment and those who are naive to treatment should be able to have the opportunity for a cure. Please don't leave hope beyond their grasp!

HepCBC Hepatitis C Education and Prevention Society

Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest		**Sofosbuvir in combination with Velpatasvir**
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		[redacted]
Email		[redacted]
Name of author (if different)		[redacted]
Patient groups contact information:	Email	info@hepcbc.ca
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	Address	#20 1139 Yates St. Victoria BC V8V 3N2
	Website	www.hepcbc.ca

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 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: publication of a monthly bulletin (the *hepc.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 coinfected (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, Vertex Pharmaceuticals, Gilead Sciences,

Janssen Pharmaceuticals, Bristol-Myers Squibb, Boerhinger-Ingelheim, 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 from patient surveys advertised through our website and our email list. Note that with each new 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 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. To avoid re-inventing the wheel, we refer you to our more detailed answers in six DAA submissions made in July, August and October of 2014, plus March (in which two separate submissions were made for two drugs from the same company), September, 2015 and November, 2015**.**

http://hepcbc.ca/wp-content/uploads/2016/04/20151111_grazoprevir_elbasvir_ZEPATIER_CADTH_redact.pdf

http://hepcbc.ca/wp-content/uploads/2016/04/20150928_ombitasvir_paritaprevir_ritonavir_CADTH_redact.pdf

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

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

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

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

http://hepcbc.ca/wp-content/uploads/2016/04/20140711_sofosbuvir_SOVALDI_Pharmacare_redact.pdf

In this section, in addition to the above, we also include two responses to our request for patient input for a previous review. These patients, both GT3, have undergone treatment several times and have been

unsuccessful. While the responses were gathered in connection with a review for another all-oral combination, they are nonetheless relevant to this one, because they reiterate the need for effective options for more difficult to treat populations (e.g. those with genotype 3).

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 69 year old male, living in BC, with GT3, who has undergone a liver transplant. He has had three previous 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."*

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 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. 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 insurers and governments rationing these cures. This is particularly frustrating for HCV patients, caregivers and doctors. Moreover, as liver disease advances, the risks 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 as they are not able to access treatment unless they have either very generous insurance plans or a lot of money.

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.

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). One of our members also attended a CTAC webinar on the combination, where data from the Astral trials was discussed. 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 Astral trials, together with other emerging data from patients who have been treated with the new DAAs, HepCBC also notes that there are issues that need to be borne in mind, along with an approval.

The combination has been shown in the Astral trials 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.

All-oral regimes are generally easier to tolerate than those containing interferon. 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.

Furthermore, we have noted the recent investigation by the 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 liver cancer 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 in our group who have taken the combination. However, data from the Astral trials, which we discussed in a webinar run by 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, ribavirin-induced side effects (e.g. anaemia, skin rashes, irritability etc.) should be expected.

As ever, we advise caution and close monitoring once the drug combination is approved in order to build up further knowledge about it, whether the additional side effects that emerge are of a serious nature or are less problematic (tolerable).

The combination should be 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). In most cases, being cured of HCV will clearly benefit a patient in terms of their overall health. However, 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.

Section 4 — Additional Information

The points we have made in Section 3.2 above support:

- Approval of sofosbuvir in combination with velpatasvir, 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 on "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.

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]

NATAP Conference reports

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 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/Directacting_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]

With thanks to [redacted] and CTAC for an opportunity to analyse the data from the Astral trials at the webinar on 2 May, 2016.

Pacific Hepatitis C Network

Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest		**Sofosbuvir / Velpatasvir**
Name of the patient group		Pacific Hepatitis C Network
Name of the primary contact for this submission:		[redacted]
Position or title with patient group		[redacted]
Email		[redacted]
Telephone number(s)		[redacted]
Patient groups contact information:	Email	info@pacifichepc.org
	Telephone	604 740 1092
	Address	PO Box 192, Roberts Creek BC, V0N 2W0
	Website	www.pacifichepc.org

1.1 Submitting Organization

Pacific Hepatitis C Network's mission is to provide a means for sharing information and coordinating mutual support and action that will strengthen the capacity of individuals and organizations throughout British Columbia to prevent new HCV infections and to improve the health and treatment outcomes of people already living with HCV. Our members include people living with chronic hepatitis C, people who are HCV antibody positive, people at-risk for hepatitis C infection, and anyone interested or concerned about hepatitis C (service providers, health care providers, family, friends).

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:*

PHCN has received project grants from Gilead Science, AbbVie Corporation, Bristol-Myers Squibb, Janssen Pharmaceuticals, and Merck Canada, for an online hep C treatment information resource.

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

The Pacific Hepatitis C Network declares no conflicts of interest in the preparation of this submission.

Section 2 — Condition and Current Therapy Information

2.1 Information Gathering

Information was gathered through an online survey that was made available from April 4th to May 4th, 2016. The survey stated that all submissions were anonymous and asked all of the questions that this patient input submission suggested, including a few general questions about the patient's health and wellbeing. Invitations to complete the survey were sent out by word of mouth, through our mailing lists, and by posting the survey's information on our website and Facebook page. We received 10 completed surveys.

2.2 Impact of Condition on Patients

Our members have described hep C as a disease that kills slowly by degrees. They describe it as a disease that is able to affect all aspects of life before it may take it.
Hepatitis C (HCV) is a serious and potentially life-threatening liver disease that can lead to liver fibrosis, cirrhosis, cancer, or failure. However, in many cases those life-threatening HCV developments may only be fought after years of worrying over the future and dealing with other HCV symptoms, which may not lead to hospital stays or liver transplants, but in their own ways, are just as debilitating.

Having the hepatitis C virus may cause numerous symptoms and affect patients differently. Symptoms may be flu-like, fever, muscle aches and pains, fatigue, loss of appetite, and/or nausea. Symptoms, reported by our members, range from “have not had hep C symptoms” to “Retired 9 years early. 5 years of brutal pain and mental disability. Liver transplant recovery. On and off ten years. Terrible nausea three times a week…”

Another member with hep C wrote: “I think I should have more energy than I do. I work at home as a freelance writer. My output seems to be declining, partly because of cognitive decline, difficulty remaining focussed, holding it all in my head, etc. And I find myself unable to manage much beyond my writing (in terms of socializing or home/garden projects).”

What the person may be experiencing is “brain fog”, a common symptom of HCV. The experience of brain fog includes difficulty thinking, remembering, understanding, and focusing. Brain fog can be disabling and impact negatively on a person’s ability to function at home and in the workplace.

People with brain fog describe having to take manual jobs requiring less cognitive function, even though this can pose other challenges if that work requires physical labour of any kind as fatigue is sometimes also a symptom of hepatitis C.

Furthermore, HCV doesn't only take a physical toll on patients, but takes psychological and emotional tolls on them and their support networks as well. This is due, in part, to the fact that hepatitis C is a disease that one often needs to wait and get sicker before receiving treatment.

Lastly, these physical and psychological tolls are often worsened by the social isolation, which comes from suffering fatigue, other HCV symptoms, and from the stigma that comes as a result of having hepatitis C, a communicable disease. One person stated, “I live in fear of people finding out.”

2.3 Patients’ Experiences With Current Therapy

Recently, there have been new hep C treatments approved for use. Patients report that these treatments are more successful, achieve sustained viral responses more often, than pegylated interferon with ribavirin alone or with either telaprevir or boceprevir, the old standard of care for some. However, some of these newer treatments still require pegylated interferon and/or ribavirin in their treatment combinations. The inclusion of pegylated interferon and/or ribavirin increases the treatment’s pill burden and is known to cause side effects so severe that they may require treatment to be stopped.

In addition, some of the newer treatments can’t be taken by those with Child-Pughs B and C. Some newer treatments still demand three or more pills be taken daily which some patients find both physically and mentally overwhelming.

Lastly, some of our members have been treated or are being treated with the new direct-acting antivirals. Some report that they were cured or that they are still in the process of treatment but that the virus is already undetectable and that they have hope that it will stay that way. Others reported that they relapsed after taking DAAs and they are now looking for other options.

Current treatments tried by our members and what was experienced:

- Pegylated interferon and ribavirin: dry mouth, fatigue, flu symptoms, lowered platelet count, lowered red blood cell count, nausea, rash or itchy skin, changed tastes
- Harvoni: headache, nausea, no side effects, treatment success, relapse after completing treatment
- Sovaldi with ribavirin: depression, fatigue, headache, loss of appetite, skin issues

2.4 Impact on Caregivers

Depression, increased family obligations, financial worries, social isolation, lack of social support, missed work, overextended / had to pick up other duties that the loved one usually helps with, stress, tiredness / lack of sleep, and feeling resentful of their partners and then guilty because they were mad at a sick person, are all things that caregivers may go through while their loved one is living with hep C and undergoing treatment.

In addition, the need for hope and the concern over health and well-being that comes with not feeling in control of one's health and future isn't experienced by just those living with HCV, but by their caregivers and their social network as well. All caregivers express concern about how hep C is impacting the health of their loved one. If their loved one hasn't yet had treatment, loved ones also experience concern about what treatment will be like.

Furthermore, one of the most difficult situations for caregivers is when treatment has failed, and their loved one is still ill, or if treatment isn't an option. A caregiver, for example, shared that when her husband was diagnosed, "the doctors just said to get his affairs in order."

Lastly, after treatment some caregivers said their lives returned to normal, especially after a successful treatment with fewer adverse effects, but not always. Sometimes their loved ones continued to experience fatigue and other post-treatment conditions that continue to impact their lives and families.

Therefore, caregivers want new treatments with higher success rates and less side effects to treat those with the virus.

Section 3 — Information about the Drug Being Reviewed

3.1 Information Gathering

Information was gathered through an online survey that was made available from April 4th to May 4th, 2016. The survey stated that all submissions were anonymous and asked all of the questions that this patient input submission suggested, including a few general questions about the patient's health and wellbeing. Invitations to complete the survey were sent out by word of mouth, through our mailing lists, and by posting the survey's information on our website and Facebook page. We received 10 completed surveys.

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:

Those with HCV have a couple of expectations for sofosbuvir / velpatasvir, however, the expectation that is foremost is that the treatment's high sustained virologic responses (SVRs) for those who are

"hard to treat" will translate into a better chance of a cure for patients and, so, enable them to start their lives anew.

Based on no experience with sofosbuvir / velpatasvir, patients expect the treatment to:

- Have a higher cure rate for patients, including patients considered 'hard to treat' (due to HIV co-infection, level of liver cirrhosis, autoimmune or other health conditions or other factors) and those who are treatment experienced but still have and can spread HCV. From someone with HCV: "Any new treatment that can help people who were not helped by other treatment will change lives."
- Offer a cure without serious side effects and be easier to take than other treatments (have less of a pill burden, etc.)
- Stop and possibly reverse liver damage and some, if not all, of the symptoms of liver damage.
- Achieve SVR and hopefully reduce their chances of developing liver cancer.
- Allow them to feel better, live the lives they want to live without constant health concerns or limitations due to hep C. If they feel they are too tried, sick, or not able to think as clearly as they have to in order to fully participate in their own lives, they want a chance to reverse that or at least make it better.
- Allow them to stop worrying. Stop worrying about health issues and the health of their loved ones/worrying about spreading the virus to their loved ones. They want to be intimate with their partners without wondering or worrying about spreading or disclosing the disease. They want to be able to do daily activities, like brushing their teeth or shaving, without wondering if their toothbrush or razor was or will be accidently used by someone else.

b) Based on patients' experiences with the new drug as part of a clinical trial or through a manufacturer's compassionate supply:

No one indicated that they have had experience with sofosbuvir / velpatasvir.

Section 4 — Additional Information

The pleas for access to better treatments that have "shortened time of treatment, less side effects, higher SVR rates, have the ability to allow patients to continue working while being treated", "the ability to cure those who have already been treated without success and the ability to cure without pegylated interferon and ribavirin", or access to treatments that may be able to bring "an end of worrying over the health of my liver", "healthier livers", "being cured faster and will not have to go thru multiple treatments", and "quick treatments that cure all GTs", are still strong, even after new hep C treatments have recently been included onto formularies.

There is a want to get better, to improve their health, and to fully participate in all that they can dream of being involved in that they haven't allowed themselves to dream of because of concerns around their hep C status.

We want to see this desire to get rid of HCV and to achieve more dreams than many with HCV currently think they can while living with hep C, be matched by Canada's ability to cure them. We think that sofosbuvir / velpatasvir, with its ability to cure multiple HCV genotypes and 'hard to treat' patients, while causing fewer side effects than other treatments, will help Canada succeed in this, succeed in helping cure Canadians living with hepatitis C.