Common Drug Review
Patient Group Input Submissions

ledipasvir/sofosbuvir(Harvoni) 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 & Prevention Society — permission granted to post
Pacific Hepatitis C Network — permission granted to post
CAPAHC, le Centre d'Aide aux Personnes Atteintes d'Hépatite C — permission not granted to post

CADTH received patient group input for this review on or before October 7, 2014

CADTH posts all patient input submissions to the Common Drug Review received on or after February 1, 2014 for which permission has been given by the submitter. This includes patient input received from individual patients and caregivers as part of that pilot project.

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

1. General Information

Name of the drug CADTH is reviewing and indication(s) of interest	Ledipasvir + sofosbuvir for chronic hepatitis C
Name of the patient group	Canadian Liver Foundation
Name of the primary contact for this submission:	[redacted]
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Permission is granted to post this submission	Yes

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 of liver disease 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 $20 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 40+ 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.

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

Dr. Sherman, Chairperson of the Canadian Liver Foundation, has received honoraria from Abbvie Corporation, Boehringer Ingelheim (Canada) Inc., Merck Canada Inc., Janssen Inc., Hoffmann-La Roche Limited, Gilead Sciences Canada Inc., Vertex and Bristol Myers Squibb.

2. Condition and Current Therapy Information

2.1 Information Gathering

In order to gather a broad range of input, the CLF invited patients, caregivers and health care professionals from across Canada to fill out an online survey modelled on the CADTH questionnaire. The survey was made available via a link on the CLF's website and 63 responses were received. Quotes from survey respondents are included in italics in various sections of this submission. Other information was provided by CLF Chairperson Dr. Morris Sherman.

2.2 Impact of Condition on Patients

Please note: *Quotes in italic text are excerpts from survey responses.*

Hepatitis C is a disease with many faces. The majority of people living with hepatitis C in Canada are adults in the 'baby boomer' age bracket who lived with hepatitis C for decades without any obvious symptoms. They are often diagnosed by 'accident' or after they start suffering from symptoms related to advanced liver disease. Once diagnosed however, patients report suffering from fear of their uncertain future and of infecting others.

"Most patients feel ashamed or judged if they have hepatitis C. They are fearful of having children and risking infecting them. They fear telling family members. It's like a big black cloud over them all the time."— health care professional treating hepatitis C patients

"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

Patients become victims of the stigma associated with hepatitis C and of the misperceptions and fears of those close to them. Many talk of being shunned by friends, family and co-workers thereby losing their social networks and support systems. They become isolated and depressed and often marriages and other personal relationships cannot survive the strain.

"The love of my life would not introduce me to her colleagues, was embarrassed by my disease and fearful of infection. She left me heartbroken."—hepatitis C patient

"I have lived with hepatitis C for 26 years. My husband died from HCV and some people have walked away because not many people understand HCV and are afraid of getting it ." – hepatitis C patient

Once patients progress to more advanced disease they find their lives unbearable due to physical symptoms which impact their ability to support themselves or even function on a daily basis. Patients report having to give up work and go on disability and struggling to complete basic household tasks due to constant fatigue and pain.

"*I suffer from extreme fatigue and ascites with weekly paracentesis and IV albumen treatment. Cannot work due to extensive water retention and muscle pain and spasms. Currently what I receive for pension makes it hard to pay my bills. I often feel depressed and sleep most of the time." – hepatitis C patient*

Chronic fatigue, mental confusion (when the liver can no longer clear the body of toxins), memory loss and mood swings mean patients who once had gainful employment or even their own businesses now live at or below the poverty line.

"Hep C since the 1970s, sick since 2001 and getting worse are the itching, nausea, fatigue, no appetite, headaches and no strength or endurance for even short times…I am financially stuck where I can no longer afford meds or treatment and have end stage cirrhosis." – hepatitis C patient

Patients also report a litany of other debilitating symptoms including nausea, headaches, sensitivities to light and food, itchy skin, abdominal pain, severe joint and muscle pain, portal hypertension, sleeplessness, slowed reflexes, psoriasis, peripheral neuropathy, osteopenia, diarrhea and muscle wasting.

2.3 Patients' Experiences With Current Therapy

Please note: *Quotes in italic text are excerpts from survey responses*.

Patients currently have two options for therapy depending upon their insurance coverage and/or the reimbursement criteria in their province: dual therapy which combines pegylated interferon with ribavirin for 24 - 48 weeks or triple therapy which combines pegylated interferon, ribavirin and a direct-acting antiviral (boceprevir or telaprevir) for 12 -48 weeks.

As both the dual and triple therapies include interferon, patients experience many of the same symptoms when undergoing treatment. The fortunate ones report having fatigue and muscle aches but others are forced to deal with a range of severe side effects which are as bad, if not worse, than the disease itself. These side effects include anemia, sleep loss, depression, mood swings, joint pain, rashes, hearing loss, skin sores, hair loss, headaches, chills, nausea, severe fatigue and excessive weight loss.

"*I have been on treatment 4 times. The trial treatment with boceprevir was the most difficult of all four. I was very sick. Nauseated, achy, angry, feeling like I was out of my head. Low white blood cells, low red blood cells, very bad skin rash. Really, really awful side effects. I was not able to work therefore I went on disability and have been living below the poverty line*." *– hepatitis C patient*

Hepatitis C treatment with dual therapy involves weekly injections of interferon and 6-8 ribavirin pills per day. Triple therapy involves the addition of even more pills – 9-12 per day for boceprevir or telaprevir – making the treatment regime complicated for both patients and caregivers to manage especially when also coping with side effects and the additional medication required to treat them.

"To date I have undergone 4 treatments, none of which have been successful…the last treatment in 2013 I was on interferon, ribavirin and Victrelis. This 48-week treatment was particularly gruelling and I was anemic almost immediately. I suffered from lack of energy, broke out in numerous rashes and my blood, platelet and hemoglobin count was much lower than normal. I was taking approximately 20 pills a day and an injection of interferon once a week. Unfortunately, I was not able to sustain my SVR." – hepatitis C patient

"The latest treatment my husband just completed was Sovaldi with pegylated interferon. This treatment was easier physically for him but harder emotionally. He became very irritable, depressed and very easily agitated. This was stressful for me as a caregiver since I never knew what mood he would be in day to day." – caregiver caring for a hepatitis C patient

As the current treatments for genotype 1 involve interferon, many patients are unable to take them. *"Current therapeutic options continue to include pegylated interferon which more than half of our patients cannot take due to underlying issues or are non-tolerant of adverse events. There are many psychiatric issues and health issues that prohibit the use of pegylated interferon. Some of these patients have been waiting for almost two decades for advancements in therapy." – health care professional treating hepatitis C patients*

Patients with the most common form of hepatitis C (genotype 1) have the lowest response rates to dual therapy – especially if they have already developed cirrhosis. Triple therapy significantly increased their odds of success. Unfortunately, access to treatment is a major roadblock.

"Current treatments are effective only in 50-65% compared to the newer therapies being effective in 95%. It is time to get rid of all interferon based therapies. The latter are associated with poor tolerance, severe side effects compared to 12 week therapies that are easier to handle. Our patients with HCV expect same access to available care as patients with HIV." -- health care professional treating hepatitis C patients

2.4 Impact on Caregivers

Please note: *Quotes in italic text are excerpts from survey responses.*

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 current 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.

"I'm always on alert for symptoms of another variceal bleed. Plans change at the last minute due to nausea, bleeding gums at night cause severe nausea on numerous mornings. Exhaustion curtails a lot of everyday activities, ascites causes him to be short of breath. So many symptoms impact every day of our lives."— caregiver for hepatitis C patient

"My husband contracted hepatitis C from tainted blood in the 1980s. The medical team indicated at the outset of my husband's illness that this journey would be a rollercoaster and that it is 'as bad as it gets'. At times we have required full-time care with family taking shifts for day and night, using holiday time and days off work. Both of us had to leave work and as he has transitioned from disability to retirement, the financial impact has been significant. Our children fear losing their father and fear the unknown. With the symptoms of the disease, sleep is difficult, both for myself and my husband. As a result, fatigue is relentless." – caregiver for hepatitis C patient.

As already noted, hepatitis C treatment with currently available drug therapies is complex and comes with many side effects which often require additional medication. For physicians and nurses, the challenges of caring and achieving a cure for hepatitis C patients are enormous. Patients require a great deal of education and counselling about treatment options and if they decide to undergo treatment it can require additional tests, lab results, forms and appeal letters before patients can actually access the therapies they need.

"For all patients, treatment algorithms require a long commitment and the boceprevir and telaprevir patients experience more side effects. The current treatment is also contraindicated for patients with advanced disease due to the medication's side effect profile. Providing care for patients on treatment often requires a team approach with specialist, nurse specialist, family doctor and in some cases, addictions and mental health. As a result of the complex algorithms and need for a team involvement, many potential health care providers opt out of treating hepatitis C patients." – health care professional treating hepatitis C patients

"If patients are on pegylated interferon, the nursing hours of care can accumulate very quickly as some have low tolerance to adverse events or are very ill during therapy. Some patients have yet to recover from the adverse events even post therapy."

3. Information about the Drug Being Reviewed

3.1 Information Gathering

As mentioned previously, the CLF invited patients, caregivers and health care professionals from across Canada to fill out an online survey modelled on the CADTH questionnaire. We received a response from one caregiver whose spouse had participated in a clinical trial for ledipasvir/sofosbuvir but also received comments from health care professionals who had treated patients with this drug combination. Quotes from survey respondents are included in italics in various sections of this submission.

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:

Among the survey respondents, 25% had not yet been treated for hepatitis C with the most common reason being the side effects associated with current treatment options. 65% had undergone previous treatment but were not able to achieve and maintain a sustained viral response (SVR). Both patients who had undergone therapy and those who had not were asked to rank the following factors with regard to a new treatment in order of importance to them:

- Ease of use
- Interferon-free
- Affordability
- Possible drug interactions
- Cure rate
- Side effects
- Length of treatment

The three factors ranked as the top three most important were cure rate, affordability and interferon-free.

Although the majority of survey respondents had not participated in clinical trials for ledipasvir/sofosbuvir, patients, caregivers and health care professionals alike forsee the potential for dramatic change in treatment efficacy and tolerability with this new combination.

"The SVR rate sounds like a miracle at 97% for both cirrhotic and non-cirrhotic patients and an 8-12 week length of treatment is a great achievement. I definitely feel that this drug should be approved for use in Canada as soon as possible. There are many people just like myself whose life depends on it."— hepatitis C patient

"We could treat most of our patients in a short amount of time, decreasing the time and money spent in hospital to follow and treat all the side effects." – health care professional treating hepatitis C patients

"This treatment would allow eradication of hepatitis C in patients for whom there has been no previous options. Health Canada did not provide label for use of Sovaldi and Galexos together so this will be the ONLY interferon-free regimen that exists for the population. It meets a huge unmet need in a population where interferon-free regimen is the only choice patients will have in eradicating the virus. In just one practice alone, I probably have at least 100 patients in this specific category." -- health care professional treating hepatitis C patients

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

A caregiver whose husband underwent treatment with ledipasvir/sofosbuvir + ribavirin as part of a clinical Phase II trial reported minimal side effects – anemia, fatigue and rash – which were much more manageable as compared to previous treatments despite her husband's more advanced illness.

"This was his third attempt at a cure. With the dosing regimen, it is easy to administer and tolerate. Viral count now zero and we're praying for zero viral count at week 12 and week 24. We must find a way to provide this treatment to others. The results are so strong – almost 100% for genotype 1a. Ethically, this needs to be available for those in end stage liver disease and for those not yet there to end the disease for them before the huge health and financial impact to the patient and to the system starts to escalate." – caregiver for hepatitis C patient

Physicians that have treated patients with ledipasvir/sofosbuvir as part of clinical trials have reported that the therapy is well tolerated and effective in curing the virus with almost no side effects.

"This is the type of treatment we need! Easier to use, side effects minimal, if any. More productivity while on treatment, less psychiatric concerns as compared to interferon. High efficacy equals more cures." – health care professional treating hepatitis C patients

4. Additional Information

With each new generation of therapies, hepatitis C treatment has been improving but to date there has yet to be an available option for those who cannot tolerate interferon. With the advent of the new combination therapy using ledipasvir + sofosbuvir, we finally have the 'game changer' patients have been desperately waiting for.

Ledipasvir/sofosbuvir does not require interferon or ribavirin which means that many patients who were ineligible for treatment due to co-morbidities or adverse reactions to interferon or ribavirin (an estimated 50% of cases) can now be treated. This will make a dramatic change to the number and variety of patients who could now undergo treatment, including patients with chronic anemia (e.g. thalassemia), autoimmune diseases, renal transplant patients and those with psychiatric conditions for whom treatment with interferon and ribavirin was contraindicated. In addition, studies have shown that ledipasvir/sofosbuvir offers an over 90% cure rate regardless of whether patients are treatment naïve, treatment experienced, cirrhotic or non-cirrhotic.

Hepatitis C is the most common indication for liver transplant but these patients still have the hepatitis C virus in their blood post-transplant. Immunosuppressive drugs allow the hepatitis C virus to more rapidly attack and damage the transplanted liver. Up until now, there were no clinically proven and approved treatment options for these patients. In some cases, the combination of sofosbuvir + simeprevir (used off-label) has been used effectively for treating patients post-transplant but it has not been widely available. If the combination of ledipasvir/sofosbuvir was approved, we would be able to prevent re-infection of the transplanted liver with the promise of substantially improved outcomes for transplants for end-stage liver disease due to hepatitis C.

Currently, patients face an average of 24-48 weeks of complicated drug regimens and significant side effects with no way of knowing going in how long it will be as it is dependent upon their response. This uncertainly weighs heavy on their minds and makes advance planning challenging for all involved. Treatment with ledipasvir/ sofosbuvir involves one pill per day (with no food requirements) for 8-12 weeks and it comes with few, if any, significant side effects meaning no time off work, no interference with family life and no difficult symptoms for both patients and caregivers to cope with.

The combination of ledipasvir/sofosbuvir holds the promise of a cure for the largest cross-section of patients of any drug therapy to date. For this therapy to make the greatest impact however, it must be accessible to all hepatitis C patients regardless of geographic location, financial status, treatment status or disease severity. The CLF believes that to effectively treat hepatitis C, the medical community must have access to the most effective treatments in order to best meet the needs of their patients. 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 except those dictated by patients' medical conditions.

For the sake of all hepatitis C patients, we call upon the CDR Committee to recommend reimbursement for ledipasvir/sofosbuvir for the treatment of hepatitis C without restriction.

Canadian Treatment Action Council

1. General Information

Name of the drug CADTH is reviewing and indication(s) of interest	LEDIPASVIR/SOFOSBUVIR (Gilead Sciences) Indication: Chronic hepatitis C infection
Name of the patient group	Canadian Treatment Action Council
Name of the primary contact for this submission:	[redacted]
Position or title with patient group	[redacted]
Email	[redacted]
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Name of author (if different)	[redacted]
Patient group's contact information:	
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Address	555 Richmond St. W, Suite 612. Toronto, ON
Website	http://www.ctac.ca
Permission is granted to post this submission	Yes

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

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

CTAC received unrestricted organizational and educational grants from the following organizations in the 2013-2014 fiscal year: Abbott/Abbvie, Boehringer Ingelheim, Gilead Sciences, Janssen, and ViiV Healthcare.

2. Condition and Current Therapy Information

2.1 Information Gathering

On Tuesday, September 30th 2014, CTAC delivered a national consultation webinar that provided an overview of the Common Drug Review (CDR) patient input process as well as key findings from the Ledipasvir/Sofosbuvir clinical trials (*NIH SYNERGY, ELECTRON, LONESTAR,* and *ION)*. This consultation webinar was presented by Adam Cook, Policy Researcher at CTAC. CTAC members, organizational partners, and interested stakeholders were invited to participate.

10 people attended the webinar. A link to both the consultation webinar video and online feedback survey were provided to webinar attendees. This link was made available through CTAC's social media outlets (ctac.ca, YouTube, facebook, and Twitter) as well as a direct link in the webinar itself. The survey was live and online from September 30th to October 6th 2014. CTAC has compiled data from the feedback survey, all respondents of which had viewed the webinar.

6 attendees completed the survey in full. 5 identified as female and 1 identified as male. 3 declared residency in Ontario and 3 were from British Columbia. 4 were hepatitis C (HCV) negative and acted as primary caregivers, while 1 respondent had achieved sustained virologic response (SVR) in 2010 after a 48-week treatment of pegylated interferon and ribavirin. 1 respondent reported being uncertain of their HCV status. No respondent had treatment experience with Ledipasvir/Sofosbuvir or Sofosbuvir alone. Accordingly, data from CTAC's previous patient input submission report regarding Sofosbuvir has served to complement this report.

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.

Also of interest to CTAC, 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.

REFERENCES:
Boccato et al. "Fibrosis progression in initially mild hepatitis C." *J of Viral Hepatits* 2006 (13)
Fontaine et al., "SVR rates and safety of triple therapy..." presented at EASL 2013

2.3 Patients' Experiences With Current Therapy

One respondent to our feedback survey had treatment-experience with the previous standard of care (daily doses of ribavirin, weekly injections of pegylated interferon, for a treatment regimen not less than 48 weeks). This respondent's experience was echoed and corroborated by other respondents when they listed their most persistent treatment side effects, "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 strongly suggests that the previous standard therapies will shortly be rendered obsolete. For example, Direct-Acting Antivirals (DAAs, such as ledipasvir/sofosbuvir) promise to shorten treatment duration, increase efficacy and tolerance, all while coming in the form of once-daily fixed-dose combinations. It is worth

noting, however, that at present, even sofosbuvir is 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."

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. It would just be so much better to use a sofosbuvir-based treatment. I suffered through virtually a whole year of treatment on the interferon regimen and it was brutal." Second generation therapies involving new DAAs such as boveprevir and telaprevir, increased SVR and often reduced treatment durations. However, as per the ADVANCE and SPRINT-2 studies, as well as the 2012 black-box warning regarding telaprevir's association with adverse dermatological events and boceprevir's association with severe anemia, the HCV community is seeking a well-tolerated treatment.

While no respondents were treatment experienced with sofosbuvir or the ledipasvir/sofosbubvir fixed-dose combination, they nevertheless expressed a positive outlook regarding the trials our webinar discussed (*NIH SYNERGY, ELECTRON Series, LONESTAR Series,* and *ION Series*). 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.

2.4 Impact on Caregivers

The majority of our survey respondents were caregivers or otherwise operated in the support network of one or more people living with HCV and/or undergoing treatment. They commonly identified the following as recurrent symptoms of both HCV and its contemporary treatments: fatigue, nausea, depression, anorexia/weight loss, possible treatment failure, and anxiety associated with side effects and the prospect of treatment failure.

One nurse from British Columbia suggested that "one of the largest challenges for individuals in British Columbia is accessing treatment to begin with. Criteria calls for evidence of liver damage before treatment can be initiated, and it is 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. 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."

This 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."

3. Information about the Drug Being Reviewed

3.1 Information Gathering

The information in this section was gathered in the same means 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?

As sofosbuvir (as the pill Sovaldi, which is 400 mg sofosbuvir) was recommended for listing by the Canadian Drug Expert Committee (CDEC) on August 20th, 2014, most respondents were positive that ledipasvir/sofosbuvir fixed-dose combination would also be approved (as this combination is 400 mg sofosbuvir and 90 mg of ledipasvir).

Again, respondents were quick to applaud this new treatment as indicative of a forward trend in treatment development away from pegylated interferon and/or ribavirin, with one caretaker lamenting, "While I work with individuals with hepatitis C in a professional capacity, it has also impacted my personal life. Two years ago I lost a friend who, like many others, could not tolerate interferon. We continued to hold on to the hope that an interferon-free treatment would become available, as we'd been hearing talk of it for some time, but sadly he missed this opportunity and passed away due to complications caused by the hepatitis C."

Several respondents noted that side effects seemed "much less severe," and when asked if they would take ledipasvir/sofosbuvir, one respondent stated "Yes! Minimal side effects, easier medication adherence, shorter treatment length." In fact, the one respondent who had treatment experience with 48 weeks of pegylated interferon and ribavirin lamented that this treatment was not available at time of their diagnosis, saying their treatment experience "…would have improved much more quickly with a lot less personal and family hardships."

4. Additional Information

CTAC continues to acknowledge and appreciate CDEC suggestions as to how to improve patient input submissions. Most recently, in response to patient input provided for Tivicay, CDEC requested more direct quotes from participants. CTAC has done its best to respond to this very agreeable request. However, due to poor response numbers, few participants, and incomplete trial data, this submission is supported from past patient input surveys (but only those involving sofosbuvir or, in the case of describing the HCV condition, our past survey regarding simeprevir, an HCV DAA).

Accordingly, CTAC would like to include the patient experiences shared by participants on social media, including online patient community forums, where several individuals share and discuss their experiences with treatments that are not market-available in Canada. Many of these forums are based in the United States and are therefore very often experienced with the treatment in question. For example, no respondent to the ledipasvir/sofosbuvir survey was experienced with that treatment. CTAC

would like greater clarification as to whether it can include these experiences in our submissions and/or direct these participants to our webinars and surveys.

Clinical trial data presently comes from international sources; the human liver is not region-specific; CDEC needs treatment-experienced patient input; allowing us access to these patient sources *will* increase our number of respondents exponentially.

This is CTAC's third such request for clarification, with past requests being made during CTAC Patient Input submissions on Prezcobix (HIV medication) and Triumeq (HIV mediation).

Gastrointestinal Society

1. General Information

Name of the drug CADTH is reviewing and indication(s) of interest	ledipasvir-sofosbuvir (brand name TBA) for chronic hepatitis C
Name of the patient group	Gastrointestinal Society
Name of the primary contact for this submission:	[redacted]
Position or title with patient group	[redacted]
Email	[redacted]
Telephone number(s)	[redacted]
Name of author (if different)	[redacted]
Patient group's contact information:	
Email	info@badgut.org
Telephone	604-873-4876 or 1-866-600-4875 (toll-free)
Address	231-3665 Kingsway Vancouver, BC V5R 5W2
Website	www.badgut.org
Permission is granted to post this submission	Yes

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-to-coast cover various digestive and liver 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, our support group meetings offer a wealth of information for those newly diagnosed with a GI 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, governments at all levels, and health care thought leaders 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 pharmaceutical companies 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). We have not received any funding from the maker of this product since 2012.

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 prepared this submission entirely independently of any outside groups or individuals.

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).

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's one thing to care for one's self, but many with HCV are also caregivers of others.

HCV becomes chronic in approximately 75% of infected people. Most chronic carriers have few or no symptoms but some report fatigue (some report extreme 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 may 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's 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 your memory and focus are impeded 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 as it is to, say, disclose a heart or lung condition. 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 healthcare 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 spread.

2.3 Patients' Experiences With Current Therapy

The current Standard Therapy 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.

Triple therapy medications, such as boceprevir and telaprevir, 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, ledipasvir-sofosbuvir is taken just once a day and can be taken with or without food.

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've failed Standard Therapy have no further options. Unless newer treatments such as ledipasvir-sofosbuvir are approved for them, they are essentially abandoned to a life sentence with this disease, or death.

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."

Hepatitis C therapy 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 shorter treatment time with fewer side effects might mean less hardship for the patient and all family members and caregivers.

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 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. Ledipasvir-sofosbuvir is just one pill a day, has no stringent food requirements, and patients take ledipasvir-sofosbuvir for as few as 12 weeks (possibly 8 weeks in some cases), 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 are not about conveniencing patients, but about enabling them to adhere to treatment and get back to their normal lives as soon as possible.

Studies have shown that interferon, which is part of current Standard Therapy, can sometimes cause or exacerbate depression. It is our understanding that ledipasvir-sofosbuvir might be administered with ribavirin but does not require interferon.

Low socioeconomic status is a risk factor for HCV, which means one of the demographics that is most susceptible to becoming infected with HCV is also very unlikely to be able to afford this new treatment on their own. While they 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.

We know this new treatment is expensive, 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 more costly, in the forms of liver transplants or other on-going, expensive medical treatments and interventions (both medical and social).

Ledipasvir-sofosbuvir is not right for everyone with HCV, but the CDR should recommend it for the patients who need it. This is a remarkable opportunity to eradicate the virus from many individuals and to prevent further spread of a malevolent infectious disease that has no vaccine.

Improved treatments for HCV like ledipasvir-sofosbuvir will have a ripple effect. Personal and professional relationships will become stronger and stigma around the disease will likely decrease. Positive education and awareness around HCV could also help decrease the spread of the disease. All of these things would ultimately lessen the financial healthcare burden, which of course is also a taxpayer's burden. The GI Society is taking action in this area and will have a video available toward the end of 2014 to assist with positive public awareness.

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 groups 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 & Prevention Society

1. General Information

Name of the drug CADTH is reviewing and indication(s) of interest	ledipasvir plus sofosbuvir – for chronic hepatitis C
Name of the patient group	HepCBC Hepatitis C Education & Prevention Society
Name of the primary contact for this submission:	[redacted]
Position or title with patient group	[redacted]
Email	[redacted]
Telephone number(s)	[redacted]
Name of author (if different)	n/a
Patient group's contact information:	
Email	info@hepcbc.ca
Telephone	250-595-3892
Address	#20 – 1130 Yates St. Victoria, BC V8V 3N2
Website	http://www.hepcbc.ca
Permission is granted to post this submission	Yes

1.1 Submitting Organization

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. Our only office is in Victoria, BC. Run primarily by volunteers living with HCV since 1996, we have activities and groups in Nanaimo, Vancouver, and Surrey, BC, and travel throughout the province doing outreach. Our representatives attend provincial and federal-level conferences and we give information and support world-wide through our website. We publish a monthly bulletin, the *hepc.bull*. We provide peer support groups, anti-stigma activities and prevention education to the general public, and general hepatitis information especially to baby-boomer, aboriginal and immigrant communities. We encourage testing among at-risk groups -- including those who are no longer at risk but may have contracted hepatitis C decades ago. We work alongside local HIV/AIDS organizations in support of co-infected people.

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, Hoffman-LaRoche, Vertex Pharmaceuticals, Gilead Sciences, Janssen Pharmaceuticals, Bristol Myers Squibb, Boerhinger-Ingelheim, and AbbVie.

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

The author of this report and three of those who contributed individual patient submissions have attended several educational conferences and meetings for which registration and travel expenses were funded by the pharmaceutical companies listed above.

2. Condition and Current Therapy Information

2.1 Information Gathering

This report was developed using data from:

(1) A patient survey advertised through our website and our email list. In total there were submissions by fifteen people living with hepatitis C (6 male, 9 female, with mean age 60 yrs, range 35 – 70 yrs, average 59.1 yrs) Genotypes 1 through 4, and all ranges of liver damage (F0 through advanced cirrhosis) were represented. Thirteen were from British Columbia, one from Winnipeg, and one from Texas, USA. The Texan was the only respondent who had actual lived experience with this drug combo.

(2) In addition, three of the above are volunteers who have actively manned HCV+ phone and email support systems for several years, and have broad knowledge of patient concerns and experiences.

(3) We've included aggregate input from one of our monthly support groups as well.

2.2 Impact of Condition on Patients

The patients in this age cohort have generally had hepatitis C for many decades. Some have been symptomatic for many years, while others are becoming symptomatic for the first time. In either case, hepatitis C is now affecting their careers and family life drastically; they think that without treatment, they will not be around much longer and must prepare themselves and their families for this. They hate the pain and the societal stigma, but especially the mental and physical changes which prevent them from working or playing as they used to. The ones that have been cured are generally celebrating the fact they are able to get their lives back, but wish they could have been cured much earlier. A few of their voices:

(F, healthcare worker): "I have progressive liver disease. The abdominal cramps and pain, the persistent physical and mental exhaustion mean that I cannot work in my profession and cannot even exercise to keep healthy. My husband does most of my personal care; he cooks and cleans the house."

(M, engineer and artist): "In 2008 I began to notice a dimming of my ability to focus on complex details. By 2011 I could no longer work, suffered sexual dysfunction, felt like the "walking brain dead", without energy or motivation, and discouraged."

(F, teacher): "I am currently not working due to extreme fatigue, inability to concentrate for a period of time, plus body and joint pain. I am not walking or exercising as I used to. I'm barely managing day to day chores and housework."

(F, housewife): "I have not experienced any physical symptoms that can be attributed to having Hep C. However, last October a liver biopsy indicated that I have progressed, in the previous year, from Stage 1 to Stage 3 fibrosis. My hepatologist has suggested that I seriously consider starting treatment. To this point I have not, because there has been nothing available that is tolerable with [consistently] positive results."

(F, housewife and singer): "Not only do I feel the social shame at having the disease, but I am experiencing physical barriers such as exhaustion and lack of energy to do anything meaningful. I forget what it feels like to be 'normal' or feel healthy, and I am losing ambition to accomplish my goals. I suffer from ascites, and when I walk or try to do anything that takes muscle movement, such as walking, I feel that my legs will not hold me up. I have learned that the tiredness comes from toxins that cannot be cleaned out by the ailing liver, which then dumps the toxins for the kidneys to deal with. I have scarring on my kidneys as a result of the hepatitis C.

Eating, too, is a challenge. My main diet is peanut butter on toast, as it is one of the few things left which I can tolerate, and actually like. I have depression when I realize it takes me forever to accomplish anything, or when I feel sick, knowing that I may never feel good again. I have no life now. I have no way to pay for the expensive treatment. If Pharmacare does not cover the cost, I have no hope. "

2.3 Patients' Experiences With Current Therapy

Every patient agrees that interferon, though it has helped many be cured of hepatitis C over the years, is like a slow and long-lasting torture; the side effects (both short and long term) are particularly debilitating, and the efficacy so low compared to current DAAs that it should no longer be given to any patient. Their voices:

"Have done pegylated interferon with ribavirin. My treatment finished a year ago and I relapsed at SVR week 12. I've never done the sofosbuvir/ledipasvir treatment; I can only speak of the interferon course which caused me to feel worse than the condition [CHC] ever did."

"I've been through treatment 4 times unsuccessfully with interferon, and recently was on a Merck DAA trial. Though I was pulled from that trial after 10 days due to a pre-condition (atrial fibrillation episode), during that time my viral load dropped from over 10 million to just 84 copies. No side-effects. In fact, after a few days I felt better than I had in years!! The Merck DAA I was on is probably similar to the drugs being reviewed here."

"I've been on 4 treatments, none of which was successful. The last treatment was in 2013 when I was on a 48-week regimen of interferon, ribavirin and Victrelis (boceprevir). This treatment was particularly grueling, and I was anaemic almost immediately. In addition to the lack of energy and extreme lethargy, I broke out in numerous rashes. I had little energy and my blood, platelet and hemoglobin counts were way out of normal range. I would not have been able to work when I was on this treatment, so it was fortunate I was on long term disability at the time. I was taking approximately 20 pills a day and an injection of interferon once a week. I was into remission at the 4th month and still in remission at the

end of treatment in December, but unfortunately, I was not able to sustain my SVR and tested positive again in May of this year."

"I am taking no therapy as I have had persistent clinical depression for 45 years. Interferon was not recommended for this reason"

A woman describes her unsuccessful 2009-2010 interferon and ribavirin treatment: "Treatment was brutal...it would have been worth it if I had cleared the virus, but unfortunately that is not the case. Side effects that were hard to deal with were weakness, loss of muscle tone (25lbs weight loss), anemia (required Epo injections) extreme emotional instability, dry cough, dry mouth, dry eyes, rash, and joint pain. Fortunately, I completed a 12-week clinical trial with Merck last week (still awaiting SVR news). This treatment was a little easier to manage. However, I still experienced fatigue, migraine, stomach upset, cramp, dizziness, and light-headedness. Being a much shorter treatment time made it tolerable."

Another woman describes her first treatment (52 weeks of interferon plus ribavirin) in 2007: "I suffered severe anemia during treatment and had to undergo a total of eight blood transfusions. HCV was non detectible at the end of treatment, however it returned one month later."

Note that these are not anomalies. Our files are full of reports such as these or worse. It is true there is a large undiagnosed baby-boomer population awaiting treatment. However there are two other large already-diagnosed populations hoping to get treated very soon: those who have never gone on treatment due to their fear of interferon (and, to a lesser extent, ribavirin), and those who have failed treatment with interferon. All of these patients are at risk of liver failure (or failure of kidney or some other organ[s] due to the HCV), liver cancer, or being put on the transplant list. The sooner all these people get treated, the more likely these expensive and debilitating HCV-related complications will be averted.

2.4 Impact on Caregivers

Caregivers of aging CHC patients are particularly vulnerable healthwise, emotionally, and financially. They too are aging, and in addition to their partner's or loved one's illness, they are often weary and may be in need of care themselves. They suffer watching the mental and physical health of their CHC partner deteriorate, and may even be the victim of their partner's short temper. Often they experience a financial double-whammy if their CHC partner has been unable to have a normal working-life, and when the partner goes through treatment or serious phases of their illness, the caregiver may have to alter his/her working life as well. Caregivers share with the CHC patient the problems of societal stigma and insecurity about whether they will be able to live independently or comfortably in what they'd hoped to be their "golden" years. Some of their voices:

"If these new drugs are not covered by my provincial plan, we will have to take some actions to cover these costs – perhaps refinancing our house or selling our house and moving into an apartment. This is one reason I have decided to rejoin the work force although I may not be ready physically or psychologically to do so – only time will tell. Having said that, I would imagine we are far better off than most patients in this situation."

"My caregiver is tired, stressed out, and unable to attend to his own interests and hobbies because of his constant need to care for me."

"On first treatment in 2009-2010, my daughter took the year out to be with me. It was hard to cook, clean and take care of myself. My relationship with my husband was put through the test. We were getting counselling. They had it rough as well as me."

3. Information about the Drug Being Reviewed

3.1 Information Gathering

Same as previous Section 2.1.

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:

These two individuals' statements echo the community's consensus about the sofosbuvir and ledipasvir combo:

"I am waiting, as I know many others are, for a treatment that does not require interferon. I often feel a lot of stressful anxiety knowing that the damage to my liver is now advancing quicker than it has previously and that I do not yet have access to a tolerable, successful treatment (such as sofosbuvir plus ledipasvir)."

"Many good things have been said about sofosbuvir, however I do not know much about ledipasvir yet. I know that sofosbuvir is a cure and if it is mixed with something without bad side effects, it will be a good combination…If this new drug is safe to use for those with cirrhosis or liver transplant, then I am ready to try it out. As long as the side effects are not as bad as those with interferon use, I am willing."

Another worry of patients is that their choice of drugs and when to take them may have long term negative consequences if they do not choose wisely: "The dilemma I am facing is that I have heard that sofobuvir may soon be approved in Manitoba. If I should take this drug and I relapse, my specialist has advised me that there is a possibility I may not be eligible for the sofobuvir/ledipasvir combination in the future."

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

Only one respondent had experience with this drug combo. His report:

"At the beginning of the clinical trial my HCV RNA was 10,870,000 IU/ML. Week 2 was 7,7400,00. Week 3 was 78. Week 4 was 'undetectable'. I had no side effects. I've been SVR for 16 months now."

"When I entered the clinical trial in April, 2012 I was very sick. I could not work, reason or think very well. My color was grey. I have seen dead people that looked better that I did. My overall state was miserable. I was diagnosed with stage 3-4 cirrhosis by needle biopsy. My doctor said that in all likelihood I would die from liver failure within 2 years. Toward the end of the 12 week treatment, I realized my brain was returning to me. I was overjoyed to feel the wheels begin to turn again. As weeks passed, I started to see things around me. My world, that I now realize had been reduced to the size of a postage stamp, started to expand. I began to feel happy, and hopeful - feelings I had not had in years. My social life was nearly dead. My wonderful, supportive wife and I began to have dinner with friends again. I

chased my lovely wife around the bedroom, and she let me catch her! I got my life back because of this new drug. I have been a successful artist for 30+ years, and am back to working nearly all day again - a far cry from sitting in a chair all day and staring out the window in a stupor.
I went to see my hepatologist in Dallas recently. Using a high resolution scan made for non-invasive observation of the liver, he was completely surprised to see no cirrhosis in my liver. There was fibrosis, but no cirrhosis."

4. Additional Information

"There are many patients with my condition – Hep C with compensated cirrhosis. Our time is running out… The rules dictated by the drug companies regarding trials are very stringent and, for the most part, seem to eliminate the patients such as myself that require the drugs as urgently as possible. Hospitals, drug companies, and governments must all work hand-in-hand very closely in their efforts to combat and eradicate this virus."

"If you have Hep C you will eventually start to feel bad, and everything about you will start to turn down, like a dimmer switch on a light. Hep C attacks your liver, and will eventually do terrible damage to it, as well as to the rest of you. However, getting rid of Hepatitis C. is not for everyone."

There is a great concern among our community that the all-but-certain approval of this drug combo is going to contain such stringent treatment criteria that many if not most of our members will be unable to access this treatment they have been waiting so long for, and which they truly see as a life or death matter. They have also been hearing recommendations to treat first those people most in risk of dying of the disease (those with F2-4 fibrosis) and those most in risk of transmitting it (IVDU). While we certainly agree that these two populations should be treated as soon as possible, two ironies stand out in this proposed triage solution:

For one, the earlier one's HCV is treated, the more likely it is that treatment will succeed, and the more quality years of life will be attained. So the idea of denying treatment until one can demonstrate significant organ damage seems not only cruel but unpractical.

The second irony is that providing treatment to IVDU while denying it to non-IVDU will only encourage those who are in recovery, or have never used drugs, to consider using drugs simply to qualify for treatment. While this may sound ridiculous, we know that others have attempted binge-drinking to raise their ALT levels to the point they are eligible for treatment. CHC patients are getting desperate, and it's really critical that ALL patients be given access to these life-saving treatments. These three patients will have the last word:

"Patients with Hep C need to be given a chance to get treatment as early as possible …The shorter period of time this is [between diagnosis and treatment], the more society will benefit from these individuals contributing to society rather than draining it over a long term."

"Please provide all of us with a treatment that is going to make us disease free. This, in the long run, will save the health care system a lot of time and money by stopping the disease before it progresses to the transplant stage…If you or your loved one had this disease, what treatment would you want?"

"Please make this available before my time runs out. Thank you."

Pacific Hepatitis C Network

1. General Information

Name of the drug CADTH is reviewing and indication(s) of interest	Ledipasvir / Sofosbuvir
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]
Name of author (if different)	
Patient group's contact information:	
Email	info@pacifichepc.org
Telephone	604 886 9539
Address	PO Box 192, Roberts Creek BC, V0N 2W0
Website	www.pacifichepc.org
Permission is granted to post this submission	Yes

1.1 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 recently received one-time project grants from Janssen Pharmaceuticals and AbbVie Corporation for the PHCN " Hep C Treatment Information Project", an online hepatitis 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:

None.

2. Condition and Current Therapy Information

1. Information Gathering

Information was gathered through an online survey between September 30th and October 6th, 2014. 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 hepatitis C. 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. We received 9 completed and 2 uncompleted surveys.

2. Impact of Condition on Patients

Abdominal pain more than once a week, "brain fog" or slow brain processing abilities, and tiredness that is bad enough that it affects one's ability to work, were all hepatitis C symptoms reported by 70% or more of our survey takers.

Nausea or vomiting more than a couple of times a week, liver cirrhosis, itchy skin, and headaches more than a couple of times a month were hepatitis C symptoms reported by 50% or more of our survey takers. Other reported symptoms were abnormally sore muscles, cryoglobulinemia, dark urine, and jaundice.

The above hepatitis C symptoms were reported, by the majority of survey takers, as not just occasional annoyances but as symptoms that effect their lifestyles, everyday living, and employment. Furthermore, 40% of those surveyed reported that these symptoms have effected their lives for over five years.

The experience of "brain fog", for example, includes difficulty thinking, remembering, understanding, and focusing. Brain fog can be very disabling, impacting negatively on a person's ability to function at home and in the workplace. People describe having to take manual jobs requiring less cognitive function, although, this can pose other challenges if that work requires physical labour of any kind as fatigue is sometimes also a symptom of hepatitis C.

In addition, our members also describe chronic and sometimes extreme fatigue that isn't remedied by sleep. Daytime resting and sleep may be necessary to just complete basic household chores, such as cooking meals, cleaning, and doing laundry. Many people must drastically reduce hours of work, or stop work altogether. For some survey takers, the fatigue they experience from their hepatitis C impacts their family life as they use what little energy they have for work and then find additional activities with family and friends too physically demanding. When asked what activities they would like to do that they were unable, someone replied that hepatitis C limits their ability to participate in evenings dancing, karaoke singing, or walking by the water with loved ones, all things that they enjoy doing. Typical comments about how hepatitis C impacts quality of life are "It all depends on the amount of fatigue I feel, if bad it is a stay at home day and I was at one time a active person" as well as "work - i am too tired for the physical demands of my work."

Finally, our members talk of the social isolation that comes from being chronically ill, but even more from the stigma that comes as a result of having hepatitis C, a communicable disease. We know that those who are socially isolated have poorer health outcomes, do not access care as quickly or as often as they should and can have more hospitalizations due to acute illness.

3. Patients' Experiences With Current Therapy

The current standard of care is pegylated interferon with ribavirin alone or with either telaprevir or boceprevir (for HCV G1). People's experiences with this treatment range from being able to continue work while on treatment to experiencing such severe side effects that they virtually cannot function and need help with basic daily living, and childcare. Having few or no side effects was a rare experience for those who had undergone the treatment.

Seventy percent of those surveyed had undergone hepatitis C's current standard of care but when they were asked if they thought that they were managing their hepatitis C as well as they could with the care and treatment resources currently available, only 50% felt that they were managing it well. Furthermore, only 14% of those surveyed experienced successful results, the same amount as those who dropped out of treatment due to its side effects. One person commented that they had "severe anemia had to be treated with several blood transfusions when drugs would have worked but they were too costly and not covered by pharmacare" and another said, "now I feel worse then before Treatment without success". These are not uncommon experiences.

Other comments address the hardships connected with the current treatment ranged from side effects to unclear medical information. Most surveyed experienced side effects on the current treatment and commented on getting anemia, itchy skin, and experiencing changed tastes. Some commented on the barriers that they faced while trying to access information about getting on treatment, such as having health conditions that didn't fit the treatment criteria and unclear instructions from their physician.

Lastly, some patients find the pill burden of taking multiple medications several times daily both physically and mentally challenging. Sid or tid dosing can involve patients waking early, staying up late, or carrying medications and food with them (risking social stigma or embarrassing explanations), and cause anxiety around missing a dose. Organizing their daily schedule around medication times can be overwhelming.

4. Impact on Caregivers

All caregivers express concern about how hep C is impacting their loved ones health and if they hadn't yet had treatment, are concerned about what treatment would be like. One of the most difficult situations, aside from ESLD, was when treatment had failed and their loved one was still ill, or if treatment wasn't an option for their ill loved one. During treatment, caregivers talked about needing to stay both alert to possible very adverse reactions while not interfering or being ''in the face" of their loved one on treatment.

The length of treatment was described as challenging, as well as the adverse effects, in terms of the caregivers having to manage more or all of the household chores, child care, and income earning on top of caring for their loved one.

This increased load could be very difficult and sometimes caregivers ended up feeling resentful of their partner and then guilty because they were mad at a sick person. 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 continue to experience fatigue and other post-treatment conditions that continue to impact their lives and their families.

3. Information about the Drug Being Reviewed

3.1 Information Gathering

Information was gathered through an online survey between September 30th and October 6th, 2014. The survey stated that all submissions were anonymous and asked all of the questions that this patient input submission suggested. Invitations to complete the survey were sent out by word of mouth, through the organization's our mailing lists, and by posting the survey's information on our website. We received nine completed and two uncompleted 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:

The expectations for Ledipasvir/Sofosbuvir are that it would address a large gap and unmet patient need. There is currently no HCV treatment available in Canada for null responders and relapsers and those who have already undergone the current standard of care. Furthermore, due to it's low toxicity and lack of significant drug interactions, it is expected that Ledipasvir/ Sofosbuvir will open up treatment to patients who couldn't tolerate previous therapies (due to HIV co-infection, autoimmune conditions or other co morbidities). We know that Ledipasvir/Sofosbuvir has also greatly improved treatment outcomes for one of the most at risk patient groups, those with cirrhosis.

Ledipasvir/Sofosbuvir is also known to be a huge improvement over current treatments because it is used to treat more than one genotype, is interferon-free, and would alleviate patient's pill burden with it's once a day dosing. So many people say things like, "I will literally die before I can get treatment right now, because of interferon. It would kill me anyways."

Some patients know that they may need to also take ribavirin, mainly those who have and that makes treatment somewhat harder to take – more than 1 pill daily, risk of more adverse affects. The balancer is that the treatment time is shorter and – the biggest deal – "The cure!!!" – is much more likely. People also expect that "their fibrosis or cirrhosis will reverse. They won't be in such risk of liver failure, cancer, or transplant. Some will be able to return to work. Quality of life of everyone will improve." Basically, people expect that Ledipasvir/Sofosbuvir, and other new drugs will, "cure Hepatitis C with little to no side effects". It's that simple.

Finally, while most people are willing to accept serious adverse effects for weeks if there's a high probability of a cure, *the expectation is that Ledipasvir/Sofosbuvir has far fewer adverse side effects.*

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

Only one survey respondent indicated that they had had experience with Ledipasvir/Sofosbuvir. They recorded abdominal pain as an adverse side effect caused by the treatment but had actually expected the treatment to be harder than it was in reality. Lastly, the respondent didn't believe that any adverse side effects were acceptable.

4. Additional Information

“Please make this available. My time is running out.” was the plea that one of our members completed their survey with. This is the reality for too many people with this virus.

Imagine having a cure and not being able to access it because it is either not covered on a public drug plan or because the criteria for getting on and staying on treatment are cost-saving rather than patient-saving measures. One respondent put it well: “The price is a huge concern. It isn't fair that most affected people cannot afford a life-saving medication in a high-income society such as Canada.”

We are concerned as well that patients may have to first undergo and fail a very challenging, longer treatment with a lower cure rate before having access to drugs like Ledipasvir/Sofosbuvir. Along with individual lives being saved and improved dramatically, early eligibility for and completion of Ledipasvir/Sofosbuvir is likely to result in financial cost savings to healthcare systems and should be considered. Ultimately, the wisest course is a reasonable balance between cost and clinical best practice in treating as many people as quickly as possible.

Centre d'Aide aux Personnes Atteintes d'Hépatite C

1. General Information

Name of the drug CADTH is reviewing and indication(s) of interest	ledipasvir/sofosbuvir(Harvoni) for Hepatitis C, chronic
Name of the patient group	Centre d'Aide aux Personnes Atteintes d'Hépatite C
Name of the primary contact for this submission:	
Position or title with patient group	
Email	
Telephone number(s)	
Name of author (if different)	
Patient group's contact information:	
Email	info@capahc.com
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Address	2065, Parthenais, suite 032 Montréal, Québec, H2K 3T1
Website	http://www.capahc.com
Permission is granted to post this submission	No

The patient group has not granted permission to post its patient input submission. When permission is not granted, CADTH will post on its website that a patient submission was received, but it was not posted at the request of the submitter.

The patient input that was provided in this submission, along with all other patient input received for this drug, is included in the summary of patient input that is contained in the posted *CDR Clinical Review Report*.