Common Drug Review
Patient Group Input Submissions

daclatasvir (Daklinza) 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.
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 March 10, 2015

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Canadian Liver Foundation

Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest		Daclatasvir (Daklinza) for chronic hepatitis C
Name of the patient group		Canadian Liver Foundation
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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 $24 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., Bristol Myers Squibb, 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.

Section 2 — Condition and Current Therapy Information

2.1 Information Gathering

Patient input collected from more than 200 previous hepatitis C surveys regarding experiences living with hepatitis C and with past hepatitis C drug treatments were incorporated into this submission. Quotes from survey respondents are included in italics in various sections of this submission. Other information was gleaned from survey responses of physicians who treated patients with daclatasvir as well as from CLF Chairperson Dr. Morris Sherman.

2.2 Impact of Condition on Patients

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

The hepatitis C virus can lurk undetected for years, even decades, without causing any obvious symptoms. As a result, progressive liver damage develops over time and can lead to cirrhosis, liver cancer and liver failure. The majority of people living with hepatitis C in Canada today are adults in the 'baby boomer' age bracket who contracted the virus many years ago before it had been identified and before the effective screening and sterilization protocols were in place both in Canada and in countries around the world. These individuals 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.

"I found out four years ago that I had hepatitis C…it has affected my relationship in a huge way. My spouse was diagnosed at the same time I was and he passed away in January 2014 due to liver cancer caused by hep C. Financially I am not able to afford any kind of treatment because I have no coverage whatsoever." – hepatitis C patient

"I have had hep C for 38.5 years...I get very frustrated living like this. It would be wonderful to find out what it is to feel normal." – hepatitis C patient

"I have had hepatitis C for over 15 years. I now have cirrhosis from the hep C. I have no energy, my liver is always inflamed and I cannot sleep anymore. It's impacting my life in a negative way. I am caring for my daughter that suffers from schizophrenia and also taking care of my 2 year old grandchild. This disease is preventing me from caring for them and if I cannot care for them who else will? They only have me." – hepatitis C patient

Hepatitis C is viewed by both the general public and many health care professionals as a disease primarily of injection drug users and it is often linked with HIV. As a result, patients become victims of the stigma associated with hepatitis C and of the misconceptions 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.

"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
While patients may live for years with few, if any, symptoms, once they 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've had hepatitis C since late 1980s and I was always ill with flu symptoms, tiredness, nausea, sensitivity to light and noise, depression, aches and physical pains. I had to quit my job and my relationship with my family went from up and down to critical. My mental health was also poor." – 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.

"unable to work = unable to have a quality life. I'm tired all the time and have brain fog. I have a limited to very low income. Very sore. Some days mental health is poor. Always stressed." – 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*.

Based on their genotype and their insurance coverage and/or the reimbursement criteria in their province, patients have the option of 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, telaprevir, or more recently, simeprevir, sofosbuvir) for 12 -48 weeks. Unfortunately, patients who cannot tolerate interferon or cannot take it due to other health issues have not had a viable treatment option until recently.

Interferon-based therapies are very hard on patients and cause the most debilitating side effects. 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 was totally disabled while on treatment. I spent 48 weeks on my couch throwing up, experiencing chronic fatigue and horrible joint pain. I developed severe anemia and should have been prescribed iron infusions by my hep C doctor at the time. Participate in normal activities? NO WAY was I able to do that!! My partner left me and I had to leave our home with my children after treatment was over. It didn't work and it has ruined my life at this stage. It was hell*." *– hepatitis C patient*

"After 14 weeks the treatment had to be discontinued due to the fact that the interferon had made me suicidal. I had very bad anemia and took Eprex injections but I was unable to work or function in any

capacity. Anxiety, depression, insomnia, hallucination and much, much more. I was completely dependent upon my parents for everything." – 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 regimen 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

The newer DAAs (simeprevir and sofosbuvir) shortened treatment and increased efficacy but still require interferon meaning that patients suffer all the same interferon-related side effects. In some limited cases where patients were able to gain access, a combination of these two DAAs proved to be very effective without interferon or ribavirin. The newest generation of hepatitis C therapies are interferon-free but few patients have had access to them except through clinical trials or in special cases where private or employer insurance plans have covered the costs.

"I underwent treatment 8 years ago and was very ill with fatigue, nausea, hair loss and in the end it was not successful. In February 2014, I was treated with the combination of simeprevir and sofosbuvir and after 4 months my viral load was down to 0. I had to take 2 pills per day and my only symptom was a slight headache. I was fortunate because my employer paid the cost but now they no longer do."— hepatitis C patient

"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 interferon-based therapies 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." – health care professional treating hepatitis C patients

Section 3 — Information about the Drug Being Reviewed

3.1 Information Gathering

We surveyed physicians who had treated hepatitis C patients with daclatasvir regarding their patients' experiences and response. Quotes from survey respondents are included in italics in the sections below. We also included relevant points from previous patient, physician and caregiver surveys regarding hepatitis C drug treatment.

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:

Daclatasvir is an oral therapy taken once a day. It can be used in combination with another BMS therapy, asunaprevir, or with sofosbuvir. This therapy does not require interferon. The length of treatment is 12 weeks which is significantly shorter than older regimens and equivalent to Harvoni and Holkira Pak. In clinical trials, the general sustained viral response (SVR) rate after 12 weeks was 80-90% for patients who had failed previous treatment or had never been treated.

Among the patients responding to our previous surveys, 28% had not yet been treated for hepatitis C with the most common reasons being fear of the side effects associated with current treatment options and the inability to pay the costs of treatment. 35% 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.

In general, patients are eager for any and all interferon-free options available as long as they are made financially accessible.

"It might offer an improvement but unless you can get it into the formulary in the next 6 months then it isn't much of an improvement in my thinking. I have stage 4 cirrhosis and don't know how long my liver will stay compensated. The more drug combos there are for treatment, the better it is. Maybe the price would go down because of the competition…when you don't have private insurance as a senior, you are sunk." – hepatitis C patient

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

Physicians treating patients with daclatasvir combined with interferon and ribavirin found that their patients still had to deal with interferon-related side effects.

"In June 2013 I started treatment with daclatasvir, asunaprevir, pegIFNa-2a + ribavirin. This treatment was for 24 weeks .Side effects were nausea, fatigue, lack of concentration, headache, mild depression. These were acceptable as long as I kept the end in sight. Because I was unable to work and could not do things that I normally did to keep my house and yard in good repair, I had to sell my house. It has now been 1 year since I completed the last treatment and I am still getting fatigued easily. My joints are not what they used to be either." – hepatitis C patient

Those that treated patients with daclatasvir + asunaprevir found that their patients had a fairly easy time with treatment and some found their quality of life improved significantly.

"Patients tolerated both medications [daclatasvir + asunaprevir] very well. There were no noticeable side effects at all. Patients felt better on the medications than they did prior to starting therapy. In fact I had a patient run/walk a half marathon while on these agents for the treatment of her hepatitis C infection. They felt the difference between these agents and the prior therapy which they had been on (pegylated interferon and ribavirin) -- it was like night and day. Several patients actually went back to work and off disability while they were on these new agents. Their response was that dramatic." – health care provider treating hepatitis C patients
"Had a very positive experience with these drugs [daclatasvir + asunaprevir]. No major adverse effects noted and it was easy for patients to take." – health care provider treating hepatitis C patients

"Patients tolerated the combination [daclatasvir + asunaprevir] very well. Essentially, they could not even tell they were on therapy. We found the combination especially successful for genotype 1b patients." – health care provider treating hepatitis C patients.

Section 4 — Additional Information

Daclatasvir is one piece of a combination therapy puzzle that can offer another interferon-free option for hepatitis C patients. Daclatasvir has been tested in combination with sofosbuvir and with asunaprevir and has showed positive results. It is a once-a-day pill that even when combined with another drug, still makes for a fairly simple regimen for patients to follow. Based on its efficacy rates, low pill burden and limited side effects, it is a welcome addition to the hepatitis C treatment arsenal.

Now that manufacturers have broken through the interferon barrier, hepatitis C treatment is getting shorter, simpler, significantly more tolerable and comes with cure rates that are approaching 100 per cent. The more medications that are licensed, the more options doctors will have to treat their patients and the greater the possibility that the increased competition will drive costs down.

Over time, hepatitis C treatment will become increasingly more personalized. No two patients are exactly alike in their disease stage, drug sensitivities, treatment history and co-existing health conditions – consequently no one drug therapy will fit the needs of all patients. Daclatasvir's ability to be combined with existing approved drugs (sofosbuvir or simeprevir) and/or an as-yet-unapproved option, asunaprevir, offers flexibility for physicians to mix and match as needed in treating patients who have previously undergone treatment unsuccessfully as well as those that have never been treated. Genotype 3 patients in particular could benefit from the combination of sofosbuvir + daclatasvir which is more effective and potentially more cost-effective than the current option of sofosbuvir + ribavirin.

Whether daclatasvir is best for any one patient however, is up to his or her doctor to decide. For this therapy to make the greatest impact, it must be accessible to all hepatitis C patients and their treating physicians 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 support the approval and reimbursement of daclatasvir for the treatment of hepatitis C without restriction.

Canadian Treatment Action Council

Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest		DACLATASVIR (Bristol-Myers Squibb) 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]
Telephone number(s)		[redacted]
Name of author (if different)		[redacted]
Patient group's contact information:	Email	[redacted]
	Telephone	416.410.6538
	Address	555 Richmond St. W, Suite 612. Toronto, ON
	Website	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.

Section 2 — Condition and Current Therapy Information

2.1 Information Gathering

On Wednesday February 25th 2015, 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 DACLATASVIR (DCV) and ASUNAPREVIR (ASV) clinical trials. These trials included reviews where either DCV, ASV, or both were examined together or in combination with other treatments. Trials discussed in our consultation included those from the UNITY Series, the ALLY Series, the HALLMARK-DUAL Study, as well as trials for BMS Study groups as led by Dr. Mark Sulkowski. This consultation webinar was presented by Adam Cook, Policy Researcher at CTAC. CTAC membership, organizational partners, and interested stakeholders were invited to participate.

8 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 February 25th to March 10th 2015. CTAC has compiled data from the feedback survey, all respondents of which had viewed the webinar.

3 attendees completed the survey in full. 2 identified as female, one identified as male. 2 declared residency in British Columbia and 1 was from Quebec. 2 were hepatitis C 9HCV) negative and 1 had achieved Sustained Virologic Response (SVR) after a treatment of pegylated interferon and ribavirin. No respondent had treatment experience with DACLATASVIR. Some patients declared a history, experience, or knowledge of Ribavirin or Sofosbuvir (which can be associated with DACLATASVIR in some cases). Accordingly, data from CTAC's previous patient input submission report regarding other HCV medications has served to complement this report. Further, notes from the consultation webinar and the attendee discussion period on DACLATASVIR and ASUNAPREVIR have been used 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.

2.3 Patients' Experiences With Current Therapy

One respondent to our DACLATASVIR survey had treatment-experience and two others were experienced as caregivers. Attendees in the discussion period of the consultation webinar declared experienced in service-provision. The treatment-experienced respondent was treated with the first generation standard of HCV care (daily doses of ribavirin, weekly injections of pegylated interferon, for a treatment regimen of not less than 48 weeks). This respondent's experience was echoed and corroborated by other respondents when they listed their concerns regarding side effects. Specifically, respondents were concerned that Ribavirin might be needed for HCV sufferers of Genotype 1A, but not for Genotype 1B. Several patients noted that they were discouraged from seeking treatment because of continued presence of ribavirin in contemporary therapy options.

Respondents 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 Direct-Acting Antivirals (DAAs) while being very concerned about the public availability and accessibility of the same. Respondents were excited that the Sulkowski study evaluated DACLATASVIR/SOFOSBUVIR in populations of patients who had previously failed first generation DAA treatment (telaprevir, boceprevir). 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.

New treatments, such as those including DACLATASVIR, 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."

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." Second generation therapies involving newer DAAs such as boceprevir 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 DACLATASVIR or treatments in which it is a component, there were some patients 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.

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. Respondents noted that while there were several side effects and a large incident rate of them associated with ribavirin, they were generally considered mild and tolerable. DACLATASVIR had an agreeable safety profile according to the consultation.

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. As one other 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 February 25th survey noted that inconsistent access to the same medication across provinces was a very serious obstacle in need of immediate reform.

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." 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 means 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?

No respondents were experienced with DACLATASVIR.

Respondents and consultation participants did identify DACLATASVIR as an effective medication that is representative of the present movement in HCV medication toward DAAs and away from older therapies (specifically pegylated interferon and Ribavirin). Many patients noted their apprehension about Ribavirin's inclusion into a DACLATASVIR/ASUNAPREVIR regimen for genotype 1B patients (as suggested by the *UNITY-2 PHASE III* trial data). Genotype 1B patients were considered to be better candidates for this treatment, with one patient noting "given the fact that I've seen SVR rates to 100% (and I have) got G1b, my life will be different knowing that I've been cured from Hep C." Patients repeatedly suggested that DACLATASVIR "without the ribavirin" was a preferable treatment regimen. However, patients also noted that both DACLATASVIR and ASUNAPREVIR looked to be components of other treatments, and not treatments in-and-of-themselves. This made it challenging to isolate and evaluate the impact of DACLATASVIR on its own, as all trial data had it paired with another treatment. Patients questioned how this would impact pill burden or whether patients would need to ask for DACLATASVIR by name or if they would be obligated to determine in which new formulation treatments DACLATASVIR might appear. Further, consultation attendees questioned the place of DACLATASVIR amidst contemporary HCV therapies like *Sovaldi* and *Harvoni* (treatments including sofosbuvir, with

which DACLATASVIR is often paired) and suggested it might be designed for more difficult-to-treat populations.

Respondents continue to recognize immediate treatment as preferable to prolonged screening or waiting to achieve a certain level of fibrosis before qualifying for treatment. As one HCV sufferer noted, "were I to obtain an SVR…my quality of life would improve immeasurably, physically and mentally. And potential long-term costs to healthcare system would of course be reduced ... and likely lower than costs of medication." As one frustrated patient commented, "My hepatologist, whom I last saw in November and next see in May 2015, is awaiting approval of public-funding (Ontario Drug Benefit) for one of the newer medications--Harvoni. (I am, btw, coinfected with HIV. Was diagnosed with both in April 2014.)"

Several respondents noted that side effects seemed common but that they appeared to be tolerable Patients suggested that many of the more serious adverse events seemed to be attributable to Ribavirin and its dermatological impacts.

Patients were reticent to recommend DACLATASVIR as a treatment regimen for everyone, preferring that this medication be recommended as a component in a co-formulation directed to those with genotype 1B and/or treatment-experienced patients with partial, null, or negative responses to pegylated interferon and/or ribavirin or first-generation DAAs like boceprevir and telaprevir. Patients reiterated that evaluating DACLATASVIR on its own was difficult as it only appeared as a component in clinical trial data.

Section 4 — Additional Information

CTAC continues to acknowledge and appreciate CDEC suggestions as to how to improve patient input submissions. Due to poor response numbers, few participants, and incomplete trial data, this submission is supported from past patient input surveys (but only those describing the HCV condition, HCV DAA medication, ribavirin treatment experience, or DACLATASVIR and ASUNAPREVIR).

Additionally, CTAC would like to thank CADTH for responding to our request for clarification as to whether we could use international patient data. We are pleased with your response and appreciate your consideration.

HepCBC Hepatitis C Education and Prevention Society

Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest		Daclatasvir
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]
Telephone number(s)		[redacted]
Name of author (if different)		
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	Website	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. We now have two offices, one each in Victoria and Vancouver, BC. Founded in 1996, and run primarily by volunteers living with HCV, 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, anti-stigma activities and prevention education to the general public, and general hepatitis information especially to baby-boomer, aboriginal and immigrant communities, and those living in rural/remote locations. 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, plus support from Rx&D 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:*
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.

Section 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 four people living with hepatitis C (one male with genotype 1a and three females with genotype 1b, with mean age 65 years). All were from British Columbia, all four had advanced liver disease (two with cirrhosis) and all three females had successfully been cured using asunaprevir+daclatasvir on a clinical trial.

(2) In addition, three of the above are volunteers who have actively manned HCV+ phone and email support systems or several years, and have broad knowledge of patient concerns and experiences; one of these is a patient-researcher who has been reading and reviewing scholarly articles about hepatitis C for twenty years.

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

2.2 Impact of Condition on Patients

In order of frequency, our members reported the condition-related symptoms below. No symptom was universally-reported; some people exhibit more symptoms than others.

Most frequently reported: Fatigue, digestive problems, muscle and joint pain, brain fog, irritability, depression, cognitive failure (concentration/attention span, speed of thought, fluency of speech, learning and memory), insomnia, slower motor reflexes, and general fear of social interaction (coupled with a fear of being stigmatized).

Also reported: Water-retention, acid reflux, gall bladder attack, lack of appetite, inability to digest many common foods, sensitivity to/avoidance of noise or light, sexual dysfunction, rapid eye deterioration, electrolyte imbalance, iron overload/imbalance, detecting chemical odours (in sweat, urine, stool, breath), anxiety, rage, hypothyroidism, Krohn's disease, seizure disorder, metabolic syndromes (fatty liver, pre-diabetes), toxic encephalopathy, ascites, and esophageal bleeds.

Day-to-day life is affected by all of the above, but in order of frequency and importance: Fatigue, muscle/joint pain, and slower motor reflexes limit both general activity and job productivity and/or effectiveness. Cognitive failure, fear of stigma and fear of social interaction limits both job effectiveness and general social interaction. Pain during movement can lead to either overuse of painkillers (which can further damage liver) or to avoidance of movement (which can lead to weight gain and other degenerative problems) Digestive and iron-overload problems limit how one shops

for and cooks food, one's diet vs. the family's diet, and when (how often) one cooks or eats, affecting this important part of family life and social interaction.

Financial difficulties ensue due to limited job possibilities coupled with the cost of controlling the disease: special food, supplements, and treatment drugs.

Feeling one must keep ones' HCV status secret, or to lie about it in order to preserve one's job or relationships is debilitating to one's spirit.

Though the symptoms above can take several decades to become obvious, for many they become manifest much earlier and are often misdiagnosed as due to some other condition as doctors do not suspect hepatitis C in non-IVDU patients.

The patients in the baby-boomer 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.

What we are struck by at this particular time, both from the individual submissions we received and from what we are hearing on a daily basis from our clients, most of whom are in the "baby-boomer" cohort, is a growing sense of desperation and despair. They are like drowning men who can see the shore, but they're swimming against the tide, and the harder they swim, the further the shore seems to be receding into the distance. They know life-saving drugs are out there if they can just hold on long enough, to keep the liver cancer and end-stage-liver-disease at bay until the drugs are covered by their provincial drug plans. They know their time is almost over -- unless they can get treated in time. They are depressed, angry, and yet - sometimes - hopeful.

The debilitating stigma is still there, but it seems HCV+ baby-boomers are generally becoming more willing to be open about their status. The promise of the new drugs has meant hepatitis C has been covered more often in the media, and the public is starting to hear the voices and see photos of people fighting the disease who are clearly not IV drug users; stereotypes which fed the stigma are being questioned. This makes it easier for people to 'come out of the closet' and seek testing and treatment. Patients and their families are at the end of their ropes, ready to do whatever it takes to get onto treatment, even if that involves exposing themselves to possible stigma at work, or amongst friends and family.

At the same time a high percentage of HCV+ people are asymptomatic while the disease does its terrible damage to their bodies. Many of them do not even know they have the disease until they receive the terrible news that they have liver cancer, or need a transplant. These people need to be tested, found, and treated as soon as possible. They are in as much danger of morbidity and mortality as those who are symptomatic.

2.3 Patients' Experience with Current Therapy

Through the Internet and support groups, patients are very knowledgeable about the side-effects of interferon, ribavirin, telaprevir, and boceprevir (while simeprevir is now publicly funded in BC and patients know it has fewer side-effects than the other protease inhibitors, few patients are taking it simply because it is still paired with interferon and ribavirin.). While recognizing and appreciating their merits, they want to avoid all of these drugs (with the possible exception of simeprevir) as much as possible.

The concept "current therapy" has become far more diversified over the last year, with patients getting treated quite differently according to genotype, their stage of liver disease, and whether they have private insurance or not. A large percentage of patients we come in contact with are being "warehoused", either by doctors or by themselves, simply rejecting the idea of taking current therapies, knowing vastly superior drugs are so close to being approved.

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) can be particularly debilitating, and the efficacy so low compared to current DAAs that it should no longer be given to any patient.

(F, 67): I am treatment-experienced, with interferon + ribavirin, 2010-2011. The treatment almost killed me and it didn't work. Later I was cured with an interferon-free, ribavirin-free BMS trial."

(M, 65): "My only experience with 'current therapy' was with a Merck interferon-free trial, but it did include ribavirin. I had a major episode of atrial fibrillation during the trial and I was taken off the trial. I am now hoping to get treated with a medication which does not interfere with my heart medications."

2.4 Impact on Caregivers

The main impacts we see on caregivers are poverty, a sense of isolation, and uncertainty about the future. Poverty is due to their untreated HCV+ partner's/parent's/child's inability to lend support to the family, followed by the increased medical expenses as their condition deteriorates. 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 often feel isolated due to stigma against those with hepatitis C and ignorance about how it is spread. They also spend much of their time looking after their HCV+ family member, or doing the chores the family member no longer can do, which cuts down on the time they used to have to socialize. There is little way to plan for a future when you don't know how long your partner will be able to live independently, or to live at all; uncertain if your partner will be able to benefit from the new HCV drugs, or if he or she will develop liver cancer or need a liver transplant before these new treatments are accessible.

Caregivers of aging CHC patients are particularly vulnerable health-wise, 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. 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 would be their "golden" years.

Section 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:

HepCBC is generally quite enthusiastic about daclatasvir. It is not used alone, but is used with one or more other drugs in a combo. A small % of patients report common side-effects such as headache, fatigue, nausea, and diarrhea (plus pruritis or insomnia if ribavirin is added), but these very rarely lead to withdrawal from treatment. Daclatasvir (no matter what other drug it is paired with) is particularly well-tolerated and safe, has extremely high efficacy even for patients with 'difficult' profiles (co-infection, cirrhosis, other liver damage, and treatment failure with 1st-generation DAAs), has a short treatment time, has minimal drug-drug interactions and presents unusually high opportunities to individualize treatment combinations.

Patients tend not to differentiate the various new drugs from one another since they're all so much better than the existing ones, and share the characteristics of being mostly tested on genotype 1, far greater efficacy, a far shorter treatment time, no interferon or needles, very few side-effects, and an extremely high price-tag. They really like the fact BMS' daclatasvir, in combination with one or more other drugs, will give some competition to Gilead's Harvoni and AbbVie's Holkira Pak, anticipating that the price of a cure will go down and Pharmacare will be more likely to cover their treatment and to get rid of the criterion of proving significant liver damage. They also are pleased that it is being reviewed on a stand-alone basis and that the manufacturer seems unusually open to daclatasvir research and its use with products from other companies. They are excited about daclatasvir's diverse uses and that it has successfully been through trials paired with asunaprevir, with asunaprevir+beclabuvir (with/without ribavirin), with sofosbuvir (with and without ribavirin), and with asunaprevir+pegylated interferon+ribavirin. They are also very pleased to see that some of the most successful trials involve its use with cirrhotics (Unity2, Ally3, and Hallmark trials), with HIV co-infection (Ally3 trial), post-transplant (Ally 3 trial), with genotype 2 (Mark Sulkowski's BMX Study Group trial), with genotype 3 (Ally3 trial), genotype 4 (Unity 2 trial) and with genotype 1 people who have previously failed treatment with pegylated interferon+ribavirin+[EITHER boceprevir OR telaprevir] (Mark Sulkowski's BMS Study Group trial). The lack of food requirements is a plus, and the number of pills per day is of little consequence to patients; the addition of ribavirin and/or interferon is more problematic though the shorter treatment time means that the side-effects will not be as serious over time. The addition of daclatasvir to Canada's hepatitis C "medicine chest" will be very exciting. Patient advocates are keenly aware of the prospect of actually being able to eradicate the disease entirely from the world, though the price will have to be greatly reduced if we are to truly eliminate it from every person in every country. Patient voice:

(M, 65): "Although I have not had 'direct experience' with daclatasvir and asunaprevir, 2 of my very dear friends were cured with it. THANK YOU. They were both GT1b. I personally could not get on a trial with daclatasvir/asunaprevir. I have 1a and failed treatment 4 times. The first 3 were with INF/RBV and the last on inhibitors. My experience on inhibitors was fantastic in terms of quality of life but a pre-existing cardiac condition acted up and I had to be pulled off. I have only hear GREAT THINGS about daclatasvir and asunaprevir both personally and from my exposure to the clinical trial reviews. I would really like to see the daclatasvir+asunaprevir combo approved as soon as possible and hopefully covered very quickly by provincial Pharmacare plans."

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

Three respondents had direct experience with daclatasvir, as genotype 1b patients in a daclatasvir+asunaprevir trial. Patient voices:

(F, 67): "After being cured, a person could lead a relatively "normal" life again. The positive side would be freedom from the damage the virus does to the liver and a possibility of the liver regenerating itself in 8 years or so. I had already failed one treatment INF plus ribavirin which had totally debilitating side-effects. Before the daclatasvir/asunaprevir trial I was F4 cirrhotic, Fibroscan 49.6 kPa. The treatment had no side-effects and I was even able to walk the half-marathon in the middle of treatment without any difficulties. One year following treatment I tested at 18 kPa so my cirrhosis is almost gone. I look forward to reversing it entirely over time."

(F, 68): "I had the IL28b TT allele, and it was no problem with the daclatasavir/asunaprevir combo. I had already gone through several other treatments unsuccessfully: INF alone for 1 year with difficult side-effects; INF+ribavirin for 1 year with even more difficult side effects but increased weight loss; low-dose "maintenance" INF for 1 year with few side-effects; and Pegasus+ribavirin for one year with very difficult side effects. Before treatment I was F2. A year later I was F1. It was great not to have to use a needle, and amazingly the treatment had no side effects. In fact, I don't believe people should expect any side effects from the new DAAs. I have slowly and steadily been getting back to what I now realize is normal. I am not in constant fear of infecting anyone. I have my energy back, and am physically able to visit my family in Australia. I am able to take on more volunteer work. If I had not retired, I would be working! Many, even most of my aches and pains are gone. I still suffer eye problems that started soon after my interferon treatments that have necessitated eye surgeries. Since being cured I have had two other surgeries that I had been postponing, since I was worried about infecting my surgeon. I have a life partner now. It really makes me happy to be able to share this!"

Section 4 — Additional Information

(F, 67): "Patients are really concerned that the prices of these drugs will be so high that CADTH (and/or provincial Pharmacare plans) will either not approve the treatment at all, or will make treatment qualification criteria very high, or will decide that treatment-naïve people should first take and subsequently fail the current standard of care (with both interferon and ribavirin) before they're allowed to take any new DAA therapy. There are no other diseases in which a patient has to prove significant damage to his/her bodily organs in order to get treated. And there are no others in which a patient has to take such clearly inferior - even harmful – treatments simply because of price."

Pacific Hepatitis C Network

Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest		Daclatasvir
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 groups contact information:	Email	info@pacifichepc.org
	Telephone	604 740 1092
	Address	PO Box 192, Roberts Creek BC, V0N 2W0
	Website	www.pacifichepc.org
Permission is granted to post this submission		Yes

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 recently received one-time project grants from AbbVie Corporation, Bristol-Myers Squibb, Gilead Science, and Janssen Pharmaceuticals for the "Hepatitis C Treatment Information Project", 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 February 2 to February 28, 2015. 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 well-being. 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, Facebook page, and Twitter account. We received 50 surveys; most were completed. As well, comments received directly from patients are included (2 patients who have treated with other new DAAs).

2.2 Impact of Condition on Patients

Hepatitis C (HCV) is a serious and potentially life-threatening liver disease that may lead to liver fibrosis, cirrhosis, cancer, liver failure, and even death. However, in many cases those life-threatening HCV developments are only fought after years of worrying over the future and rearranging their lives because of HCV and its symptoms, which may not lead to hospital stays or liver transplants, but, in their own ways, are far more debilitating.

Hepatitis C symptoms are numerous and affect patients differently. Symptoms, reported by our members, range from "have not had hep C symptoms" to "having muscle and joint pain" to being "seriously affected by nausea, vertigo, brain fog, itchy skin (especially thighs), arthritic knees and fingers." Furthermore, when asked if their HCV symptoms affected their daily living, someone replied, "I eat well and run and exercise and usually try to ignore the pain/discomfort."

Another 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 hep C. The experience of "brain fog" 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 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. Comments received about how HCV impacts quality of life were: "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", and "I am extremely exhausted most of the time."

The above quote not only touches on "brain fog", but it also expresses the uncertainty, helplessness, and worry, that often surrounds hep C. HCV doesn't only take a physical toll on patients, but takes psychological and emotional tolls on patients and their support networks as well. This is also due, in part, to the fact that it is a disease that one often needs to wait and get sicker before receiving treatment, but it's also a disease that people die of before being able to find a treatment able to cure their hep C. One member wrote: "To be rid of something that has the potential to destroy one's body would have profound physical and psychological benefits."

Another member wrote about always feeling like their health is unreliable and wondered if they would have taken more chances, in their social life and their career, if they weren't always concerned that their health wasn't up to the challenge.

Lastly, these physical and psychological tolls are often worsened by the social isolation, which comes from suffering fatigue, other hep C symptoms, the worry of passing HCV on, and from the stigma that comes as a result of having hepatitis C, a communicable disease. Someone stating that they are “afraid of passing this on so no intimate contact since being diagnosed. Makes for a very lonely existence.” We know that those who are socially isolated have poorer health outcomes, do not access care as quickly or as often as they could, and can have more hospitalizations due to acute illness.

2.3 Patients’ Experiences With Current Therapy

The current standard of care is changing. It was pegylated interferon with ribavirin alone or with either telaprevir or boceprevir (for HCV genotype 1). Patients’ experiences with this treatment range from being able to continue work while on treatment to experiencing such severe side effects that they virtually couldn't function and needed help with basic daily living and childcare. However, experiencing few or no side effects wasn't an experience described by anyone who completed our survey.

What was mainly described, by those who completed our survey, was a treatment that didn’t have very good success in 'curing' their hepatitis C and that included side effects that made it difficult to complete. Some reported severe anemia and others said that after completing treatment with interferon and ribavirin they turned out to be non-responders and their HCV reappeared.

Additionally, some patients find the pill burden of taking multiple medications several times daily both physically and mentally challenging. Some treatments 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.

However, a few of our members have been treated or are being treated with direct-acting antivirals. Some reported 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 the DAA and are now looking for other options.

2.4 Impact on Caregivers

The need for hope and the worry and 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 as well. All caregivers express concern about how hep C is impacting the health of their loved one and if they hadn’t yet had treatment, concern also about what treatment will be like.

One of the most difficult situations 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.”

When treatment was an option, caregivers talked about the complexity of needing to stay both alert to possible very adverse reactions while not interfering or being ‘’in the face” of their loved one on treatment.

Furthermore, treatment not only affects the lifestyles of the patients but the lifestyles of their loved ones as well. For example, suffering from treatment side effects decreases what one can do and increases the workloads, such as household chores and income earning, of others. A caregiver, when asked about her experience while her husband was taking treatment, explained that she had to quit her job to care for her husband while he was on treatment as he experienced variceal bleeding which worried her, but when she did so she felt that there weren't enough social supports to support her.
Some caregivers end up feeling resentful of their partners and then guilty because they were mad at a sick person.

In addition to feeling overwhelmed and resentful, they also reported suffering from depression, lack of sleep, and additional stress, while their loved one was seeking treatment.

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.

Section 3 — Information about the Drug Being Reviewed

3.1 Information Gathering

Information was gathered through an online survey that was made available from February 2 to February 28, 2015. 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, Facebook page, and Twitter account. We received 50 surveys; most were completed. As well, comments received directly from patients are included (2 patients who have treated with other new DAAs).

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 daclatasvir, however, the expectation that is foremost is that the treatment's high sustained virologic responses (SVRs), which have been reached in clinical trials, when daclatasvir is combined with other drugs, will translate into a better chance of a cure for patients and, thus, enable them to start their lives anew.

In response to being asked what their expectations for the new drug are, one of our members wrote: "A cure means a return to normal life. Ability to work full time, think clearly and have intimate contact with others. No more worries about dying decades too soon."

Due to its low toxicity and lack of significant drug interactions, it is expected that daclatasvir will open up treatment to patients who couldn't tolerate previous or can't tolerate current therapies (due to HIV co-infection, autoimmune conditions, or other factors). It also looks like daclatasvir has also greatly improved treatment outcomes for those with compensated cirrhosis who are treatment-naive and treatment-experienced.

Daclatasvir, in combination with other drugs, has also been tested in clinical trials and have resulted with high SVRs without interferon and, thus, another treatment can be free of interferon's side effects. When asked what they hope daclatasvir can achieve, people say things like: "Any new treatment that can help people who were not helped by other treatment will change lives."

One member told us directly that they are detectable again (genotype 2) one year after successfully completing sofosbuvir and that they are looking to other new DAAs to treat with for a final cure. Another patient echoed that sentiment, saying that their genotype 2 infection was successfully treated but they are keeping an eye on their viral load and hoping that if they relapse, other options will be available.

In addition, people also expect that "their fibrosis or cirrhosis will reverse. They won't be at 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 daclatasvir, 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 daclatasvir has far fewer adverse side effects than past treatments.

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 had had experience with daclatasvir.

Section 4 — Additional Information

"Shortened time of treatment, less side effects, higher SVR rates, the ability to continue working while being treated", "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 all now expected of hepatitis C treatments.

There is a want to get better, to improve one's health, and to fully participate in all that they dream of being involved in or that they haven't allowed themselves to dream of because of concerns around their hep C. There is hope that new and greatly improved treatments are coming and that the treatments will be available to them.

However, we are concerned that treatments, such as daclatasvir, that achieve different SVR rates for different population groups from approved treatments or hep C treatments currently ahead of daclatasvir in the drug pipeline, will remain unaffordable and unreachable. We are concerned as well that some patients may have to first undergo and fail very challenging, longer treatments with a lower cure rate before having access to drugs like daclatasvir.

Along with individual lives being saved and improved dramatically, early eligibility for and completion of treatments with daclatasvir are 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.