Common Drug Review
Patient Group Input Submissions

elbasvir/grazoprevir (Zepatier) for the treatment of 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.
GI (Gastrointestinal) Society — permission granted to post
HepCBC Hepatitis C Education and Prevention Society — permission granted to post
Pacific Hepatitis C Network — permission granted to post

CADTH received patient group input for this review on or before November 12, 2015.

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

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

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

Canadian Liver Foundation

Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest		Grazoprevir + elbasvir for chronic hepatitis C
Name of the patient group		Canadian Liver Foundation
Name of the primary contact for this submission:		[redacted]
Position or title with patient group		[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 for Canadians of all ages living with or at risk of liver disease. The CLF is the sole lay organization in Canada directing funds specifically for liver disease research and has invested more than $23 million in the scientific search for causes, preventative measures and potential treatments for liver disease, including viral hepatitis. As the largest community organization dedicated to liver disease, the CLF reaches over 250,000 Canadians through our public and professional education programs, patient support programs and other fundraising and outreach efforts. Over the past 45+ years, the CLF has invested more than $50 million in health education and prevention programs.

1.2 Conflict of Interest Declarations

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

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

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

To gather a broad range of input for numerous hepatitis C-related CADTH submissions, the CLF has repeatedly invited patients, caregivers and health care professionals from across Canada to fill out online surveys modelled on the CADTH questionnaire. The more than 400 responses to these various surveys have been used in compiling the feedback for this submission. Quotes from survey respondents are included in italics in various sections of this submission.

2.2 Impact of Condition on Patients

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

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

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

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

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

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

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

"*I have had HEP C for 38.5 years. I have sensitivities to dairy, wheat, tomatoes, and sugar. Food becomes an issue a big issue for me. I also have low platelets, so I tend to get nosebleeds, bruise easily and have to be careful not to cut myself or injure myself in any way. I have lost interest in gardening because I just don't have the energy for that any more. I do not always sleep well at night; I have to be careful that I don't eat wrong foods as they keep me up as well. I have to be careful not to get colds because my immune system is low. I also get itchy because of bile in the blood and although I take a medication for it, the itch will keep me awake at night especially. I get very frustrated with living like this. It would be wonderful to find out what it is to feel normal." – hepatitis C patient*

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

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

2.3 Patients' Experiences With Current Therapy

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

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

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

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

Patients with genotype 4 have limited treatment options as the direct-acting antiviral therapies noted above are only reimbursed for genotype 1 patients in most provinces. Gentoype 4 patients, depending upon their insurance coverage and/or the reimbursement criteria in their province, are primarily eligible for treatment with dual therapy which combines pegylated interferon with ribavirin for 24 - 48 weeks. Dual therapy involves weekly injections of interferon and 6-8 ribavirin pills per day. Interferon has well documented and often brutal side effects. 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. Many patients, regardless of genotype, are unable to take interferon-based therapy due to contraindications.

2.4 Impact on Caregivers

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

The burden of care for patients with hepatitis C often falls to spouses, parents and adult children. The symptoms of hepatitis C and the side effects of interferon-based therapy can leave patients completely dependent and unable to contribute financially, physically, psychologically or emotionally to the household or the relationship. Caregivers report having to endure their loved one's mood swings, dietary problems, lack of energy and concentration while shouldering the responsibility for managing doctor's appointments, drug regimens and all household responsibilities. Due to a patient's inability to work, caregivers often become the sole income earner which adds even more stress. As the patient's symptoms and behaviour become more difficult to manage, families and marriages can break apart due to stress, financial difficulties and social isolation.

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

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

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

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

"Treatment was March - August 2014 (third attempt at cure). All side-effects were manageable and so much less than any other regimen, despite his F4 cirrhosis and increasing MELD and symptoms. Anemia,

fatigue, rash, leg cramps, and bowel disturbance were some of the side-effects, with the latter likely a result of the disease, not the medication. With the dosing regime, it is easy to administer and tolerate. He took the regime with ribavirin in the Gilead trial, and as a result, itchy rash was a symptom. Compared to the other two treatments he endured - first was 2006/7 with Ribavirin/Interferon and the second in 2012 with Telaprevir/Interferon/Ribavirin, this treatment was very manageable. The first was very difficult, the second try almost led to his death - became very very ill" – caregiver for hepatitis C patient

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

Section 3 — Information about the Drug Being Reviewed

3.1 Information Gathering

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

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

Hepatitis C genotype 1 patients have been the beneficiaries of a wave of new interferon-free direct-acting antiviral treatment options which offer up to a 100% cure rate. These patients still face challenges in accessing these therapies due to reimbursement criteria and time delays in approval but there are many more patients who can finally look forward to a prospect of a cure than ever before. There are however some patients who are being left behind -- patients with chronic kidney disease who are unable to take ribavirin, those co-infected with HIV or those with other complicating health conditions which make them ineligible for currently approved treatments. These difficult-to-treat patients need more options that will allow their doctors to strike the delicate balance involved in effectively treating their hepatitis C without causing their other health conditions to worsen.

According to physicians who have treated some of the hard-to-treat patients with grazoprevir/elbasvir, those with genotypes 1 and 4 and chronic kidney disease experienced only mild side effects, were able to tolerate the therapy well and were successfully treated.

For genotype 4 and 6 patients, the treatment options to date have been very limited. Genotype 4 patients can expect a 40 per cent or less success rate on dual therapy with pegylated interferon + ribavirin. Genotype 6 patients can expect a higher success rate of 80 per cent. In both cases however, patients have to deal with the harsh and debilitating side effects associated with interferon for anywhere from 24 to 48 weeks. Recently, the interferon-free combination of ombitasvir/paritaprevir/ritonavir (brand name: Technivie) has been approved for genotype 4 patients

but there have been concerns about treating patients with advanced liver disease with this therapy. In the U.S., the FDA recently asked for label changes warning of potential liver injury associated with both ombitasvir/paritaprevir/ritonavir + dasabuvir (Holkira Pak)_ and ombitasvir/paritaprevir/ritonavir (Technivie).. . This week Health Canada has issued a similar warning against using these therapies for patients with moderate hepatic impairment (Child-Pugh Class B) or severe hepatic impairment (Child-Pugh Class C).

Hepatitis C patients, regardless of genotype or additional health conditions, and the physicians that treat them, are looking for a safe, effective, affordable, easy-to-take, and, above all, interferon-free, therapy with the highest possible cure rate.

"All oral, short duration, good success rate and few adverse events would be the ideal treatment for all patients infected with CHC. If we could treat all patients infected, maybe we could put a stop to the virus worldwide. We must start somewhere in order to attain this goal. I've been doing hepatitis support for 17 years, and my heart breaks every time a patient passes away from this disease. I feel helpless when no therapies are available due to the seriousness of their illness. Some have young children at home, spouses, family, etc. They leave us too early in their life. Let's put a stop to this and cure them of their hepatitis C once and for all. Let's stop the spread before others succumb to their illness." – health care professional treating hepatitis C patients.

Section 4 — Additional Information

Genotype 1 patients make up the majority of hepatitis C patients in Canada and stand to benefit the most from the recently approved, new generation, interferon-free therapies. These dramatic breakthroughs have made a significant change in duration, tolerability and effectiveness of treatment but it still requires matching the appropriate treatment regimen with the appropriate patient. Hepatitis C genotype 1 patients are not homogeneous and cannot be treated as such. In an ideal world, physicians would have access to all approved therapies so they could customize treatment to achieve the best possible outcome for each patient. It makes sense therefore to approve grazoprevir/elbasvir in order to add one more tool to their toolbox for the benefit of patients for whom other treatments are not the best fit.

As noted earlier, genotype 4 and 6 patients have had few treatment options to date. Genotype 4 is the most common genotype amongst immigrants in Canada from Egypt and the Middle East. The CASL Consensus Guidelines for Hepatitis C recommend ombitasvir/paritaprevir/ritonavir with or without ribavirin or sofosbuvir/ledipasvir for the treatment of genotype 4 but neither of these treatment options have been approved for reimbursement by the provinces for this genotype. For genotype 6, the guidelines recommend sofosbuvir/ledipasvir but once again, there is no coverage for this therapy in this genotype. Grazoprevir/elbasvir has been shown to be effective in both genotypes 4 and 6 which would make it an excellent addition to the treatment arsenal for these patients pending reimbursement approval.

One day, there may be a single therapy that will work for all genotypes and their associated health conditions. In the meantime, hepatitis C treatment is like putting together a puzzle. It is critical that patients and their physicians have access to the widest range of treatment options in order to find the right match for their specific disease profile. Regardless of their genotype, hepatitis C patients should have the opportunity to undergo interferon-free therapy no matter their geographic location, financial

status, treatment status or disease severity. Physicians are the most equipped to decide what treatment option holds the greatest odds of a cure for their patients so there should be no restrictions on access.

We therefore call upon CDEC to recommend reimbursement for grazoprevir/elbasivr for the treatment of hepatitis C genotype 1, 4 and 6 without restriction.

Canadian Treatment Action Council

Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest		MK2 (grazoprevir + elbasvir), manufactured by Merck. Pre-NOC, but intended for the treatment of chronic hepatitis C infection
Name of the patient group		CTAC
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	416.222.2822, XT 222
	Address	555 Richmond St. W, Ste 612
	Website	www.ctac.ca

1.1 Submitting Organization

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

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

1.2 Conflict of Interest Declarations

CTAC received unrestricted organizational and/or educational grants from the following organizations in the 2014-2015 fiscal year: Abbott/Abbvie, Gilead Sciences, Janssen, and ViiV Healthcare.

Section 2 — Condition and Current Therapy Information

2.1 Information Gathering

On Monday November 2nd, 2015, CTAC delivered a national consultation webinar that provided and overview of the Common Drug Review (CDR) patient input process as well as key findings from the MK2 (grazoprevir/elbasvir) clinical trials (C-Edge, C-Worthy, and C-Salvage). This consultation was presented

by Adam Cook, Policy Researcher at CTAC. CTAC members, organizational partners, and interested stakeholders were invited to participate.

5 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 to stakeholders 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 November 2nd to November 11th. CTAC has compiled data from the feedback survey, all respondents of which had viewed the webinar.

3 Respondents completed the survey in full. 2 identified as Female and 1 identified as Male. One each were from the provinces of BC, MB, and ON. One each identified as HCV-negative, HCV-positive, and having achieved SVR on Boceprevir. 1 respondent identified as a null-responder who had failed 2 courses of pegylated interferon and ribavirin. 1 respondent identified as a caregiver for someone living with HCV.

No respondent was treatment-experienced with MK2, as this medication has not received a Notice-of-Compliance from Health Canada and is therefore not authorized for sale or use in Canada. CTAC reiterates its repeated call to CADTH to take leadership in connecting clinical trial participants with patient groups and/or the CDR process. Without this leadership, CADTH is asking patients about a drug they do not know and have not tried, thereby compromising Patient Input and the CDR as a whole. We cannot overstate how important this reform is to the legitimacy of the CDR, its ability to defensibly state that it acknowledged Patient Input, and to CTAC's continued participation in this process. Clinical trials deploy treatment-experienced patients in the hundreds; CTAC is forced to write Patient Input reports with the input of a fraction of that number, and all of them treatment-naïve. If the CDR truly respects the patient voice, we anticipate action on this issue immediately.

Due to the lack of treatment experienced patients in Canada, our ability to wholesomely complete this Patient Input report is seriously compromised. Accordingly, we have used Patient Input, anecdotes, experiences, and data, from some of the 10 Patient Input submissions and Therapeutic Reports CTAC has submitted in 2015, to complement this report, as appropriate.

2.2 Impact of Condition on Patients

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

A hearty and unique virus, HCV is transmitted through blood-to-blood contact. While approximately 20% of people infected will pass the virus naturally, approximately 80% will not and the presence of the virus will develop into a chronic HCV infection. Asymptomatic for much of its cycle, HCV infection slowly causes significant liver damage, contributing to fibrosis, cirrhosis, and even liver cancer. Past strategies for treatment suggested a wait-and-see approach to determine if the virus was passed naturally, or to confirm that liver damage progression (fibrosis) was fast and severe enough to demand treatment (metavir score > F2). New evidence, however, suggests that more than 60% of all HCV sufferers will sustain fibrosis and incur liver damage necessitating quick and effective treatment. Left untreated for long periods of time, chronic HCV can lead to decompensated liver cirrhosis or hepatocellular carcinoma, the leading causes of liver transplantation in Canada. Consider the impact of this strategy to

special populations in Canada, as one caregiver respondent noted, *"As an example, an individual I am working with had taken great strides to achieve stability in her life with the hopes of getting on hepatitis C treatment. She is in supportive housing, and had stopped her substance use. After visiting the hepatitis C clinic and being told she was not eligible because her liver was too healthy, she questioned why she had put all that effort into maintaining sobriety and began her substance use again, putting her housing at risk. She had all the pieces lined up, and would have been in a good spot to initiate treatment, however this news has sent her on a path that may indeed lead to liver damage, but also a more chaotic situation that would not be conducive to an easy treatment for her."*

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

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.

Additionally, CTAC and its stakeholders are becoming more concerned about increased patient reports of *Extra-Hepatitic Manifestations of HCV*, or impacts and outcomes of HCV that are not specifically related to liver health. These include, but are not limited to: cognitive impairment, "brain-fog," impacts to memory, joint pain and swelling, increased mood irregularity, and significant fatigue. We implore CDEC to consider these elements of living with HCV as well as to discuss the significant lack of reporting on these symptoms in clinical trials for contemporary treatments of HCV.

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

Two respondents in this survey identified as a either a Patient or Caregiver for someone living with HCV and had treatment experience or caregiver/service-provision experience with previous standards of care (pegylated interferon with ribavirin; and boceprevir) and these respondents continued to report

concerns regarding side effects associated with ribavirin. Ribavirin still has a place in contemporary therapies, depending on treatment history and genotype, and its inclusion in many therapies today was an issue. 1 Respondent reported that they would not be using any future therapy including ribavirin because "*my specialist told me there is no way I could ever use a treatment method that includes Ribavirin...my system just can't handle it."* While another reported that ribavirin had been traditionally underestimated in its impact to patients, calling its side effects *"…more severe. Ribavirin can do nasty things to you."*

With that in mind, respondents were very excited to see that while RBV still has a place in re-treatment, its use in MK2 appeared to be very limited and only in specific instances.

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.

Concerns about the continued persistence of side effects in contemporary treatments were a regularly reported concern of all patients, 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."*

In the post-webinar discussion, attendees made note that HCV treatments seem to be becoming more appropriate with Real-World Patients, specifically, that MK2 trials included participants who were co-infected with HIV; participants with renal impairment; and participants with compensated cirrhosis.

2.4 Impact on Caregivers

One respondent identified as a caregiver providing services to people living with HCV. They 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 were pleased with the safety profile of 2D, but were still very concerned with the continued inclusion of ribavirin in contemporary therapies.

Attendees to the webinar engaged in a thoughtful discussion following the webinar, where access and eligibility requirements became recurring topics. Access to treatment in Canada can be complex considering the 19 separate federal public plans available to over 11 million Canadians who depend on them. This places great pressure on caregivers and service providers to help navigate patients through a complex, dynamic, and often opaque treatment landscape as well as call upon them to begin a quick and coherent uptake of changing treatment requisites and eligibility criteria. 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."* Almost all respondents to the December 10th survey

noted that inconsistent access to the same medication across provinces was a very serious obstacle in need of immediate reform. It was reiterated that this discrepancy in access to federally approved medicines across all Canadian provinces was an uncomfortable and counter-intuitive challenge to their understanding of the Canadian health care system. What is the biggest challenge facing caregivers regarding new HCV medications? *"Getting hold of it."*
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 respondent had any experience at all with MK2, and most had never heard of it. This is a regular issue in providing patient input in Canada. We call upon CADTH to take leadership in connecting treatment-experienced, clinical trial participants with patient input-submitting organizations like CTAC. The Canadian Drug Experts Committee (CDEC) would be better served in their challenging deliberations by having patient input reports representing as many people as possible. In many cases, new drugs have been available in other foreign or private markets, or clinical trials have produced treatment experienced patients in the hundreds (sometimes thousands), but this data is lost to the patient input gathering process and our work is compromised as a result. If CADTH is earnest and courageous about taking seriously its commitment to evidence-based decisions, we challenge them to take leadership in addressing this very serious and impactful gap in the patient input process.

Despite this incomplete process, many patients expressed hope for MK2 as a new treatment for HCV. This can be demonstrated in the below quotes from the MK2 feedback survey:

- *"it sounds more effective than previous treatments"*
- *"What I hope will be different now. A social life that doesn't require all my time and energy to attend appointments with medical professionals. I hope my energy levels will gradually increase ànd that I will be able to actively participate in life again. Especially with family and friends. I have not been able to see my family in Alberta for a long time. I miss them terribly. Also perhaps some part time employ utilizing my skill set. I have a new lease on life :)"*
- *"it would seem a far easier treatment to tolerate."* (than boceprevir or peg-int/rbv)

Section 4 — Additional Information

CTAC continues to acknowledge and appreciate CADTH and CDEC suggestions as to how to improve patient input submissions. CTAC was extremely pleased to be involved in stakeholder feedback interviews conducted with CADTH's Impact and Evaluations Advisor, Andrew Dzuba, in April of 2015. CTAC would love to hear of any further work or initiatives in response to that feedback (this is our second request to hear follow-up from the April consultation process). Further, CTAC is excited and motivated to discuss revisions, reform, and refinements to the patient input process that can better represent the patient voice as well as improve the work of not only submitting organizations, but the CDR as a whole.

GI (Gastrointestinal) Society

Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest	grazoprevir-elbasvir (brand name TBA) for chronic hepatitis C
Name of the patient group	GI (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)	
Patient group's contact information: Email	[redacted]
Telephone	604-873-4876
Address	231-3665 Kingsway Vancouver, BC V5R 5W2
Website	www.badgut.org

1.1 Submitting Organization

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

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

Our free BadGut® Lectures from coast-to-coast-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. Please see our recent video on Hepatitis C here: http://www.badgut.org/information-centre/multimedia/hepatitis-c-video/

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 the GI Society's Medical Advisory Council (made up of GI/liver health experts only) reviews and approves. We do receive funding from Merck, but not for the completion of this document, or any related issue.

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.

Section 2 — Condition and Current Therapy Information

2.1 Information Gathering

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

2.2 Impact of Condition on Patients

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

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

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

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

The GI Society represents patients with a variety of gastrointestinal and liver conditions, almost all of which are highly stigmatized. It is not easy to talk about an infection with hepatitis C 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 health care burden. Additionally, as those with hepatitis C carry on with the virus ravaging their bodies, they are more likely to spread the disease to others. By eradicating the virus from infected individuals, we can prevent its spread.

2.3 Patients' Experiences With Current Therapy

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

Triple therapy medications, such as boceprevir and telaprevir, combined with ribavirin are an improvement over dual therapy, but they come with additional side-effects and require a patient to adhere to a regimen of many pills (as many as 12) taken throughout the day, often with specific food requirements. In contrast, patients undergoing treatment with grazoprevir-elbasvir combination take a single tablet each day.

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

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

2.4 Impact on Caregivers

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

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

Section 3 — Information about the Drug Being Reviewed

3.1 Information Gathering

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

3.2 What Are the Expectations for the New Drug or What Experiences Have Patients Had 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. Grazoprevir-elbasvir is just one pill a day, has no stringent food requirements, and patients take it for as few as 12 weeks, further minimizing potential side-effects. In addition, the sooner a person is effectively treated (i.e., **cured**), the less chance they have of inadvertently infecting someone else.
These factors enable HCV-infected patients them to adhere to treatment and get back to a normal live as soon as possible.

Grazoprevir-elbasvir offers hope to patients who are infected with a range of HCV genotypes, those who failed on previous treatments, those who have chronic kidney disease, and those who are also infected with HIV.

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

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

Grazoprevir-elbasvir might not be right for everyone with HCV, but the health technology assessment should weigh the new benefit of a cure as a paramount goal of treatment for the patients who need it. This is a remarkable opportunity to eradicate the virus from many high-risk individuals and to prevent further spread of a malevolent infectious disease that has no vaccine.

Improved treatments for HCV like grazoprevir-elbasvir 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. We are doing our part to educate on hepatitis C with our video. Please take time to view the video as part of this patient input submission.

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

HepCBC Hepatitis C Education and Prevention Society

Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest		Merck's combination: grazoprevir/elbasvir
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)		
Name of author (if different)		[redacted]
Patient group's contact information:	Email	info@hepcbc.ca
	Telephone	250-595-3892
	Address	#20 1139 Yates St. Victoria BC V8V 3N2
	Website	www.hepcbc.ca

1.1 Submitting Organization

Founded in 1996, HepCBC is a registered non-profit society run by and for people infected with, or affected by, hepatitis C. Our mission is to provide education, prevention and support to those living with HCV. We have an office in Victoria and have recently opened another in downtown Vancouver, BC. Most of our staff are volunteers with experience (either past or present) with hepatitis C. We also employ 4 contractors on part-time, short-term contracts. We run activities and groups in many areas of the Lower Mainland and travel throughout the province doing outreach. Our representatives attend provincial, federal and international conferences and participate at health-related events. In addition, we provide support and information globally through our website. Other activities include: publication of a monthly bulletin (the *hepc.bull*), plus peer support, anti-stigma activities and prevention education to the general public, general hepatitis information, particularly to baby-boomer, aboriginal and immigrant communities and those living in rural/remote locations. We support and encourage testing among at-risk groups, including those who are no longer fall into this category but may have contracted hepatitis C decades ago, either through the blood system (whether in Canada or abroad) or through recreational drug use. We also work alongside other organizations, including local HIV/AIDS organizations to support those co-infected (for example with hepatitis B and/or HIV).

1.2 Conflict of Interest Declarations

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

HepCBC Hepatitis C Education & Prevention Society has received funding—for hepatitis C-oriented projects such as publishing educational materials, organizing educational forums, attending and presenting at educational conferences, advertising in newspapers (events and hepatitis C patient awareness), and holding awareness activities—from the following pharmaceutical companies over the last four years: Merck Pharmaceuticals, Hoffman-LaRoche, Vertex Pharmaceuticals, Gilead Sciences,

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

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

One of us who has completed patient submissions and both of the authors of this report have attended several educational conferences and meetings for which registration and travel expenses were funded by the pharmaceutical companies listed in (a).

Section 2 — Condition and Current Therapy Information

2.1 Information Gathering

The information was generated using data from:

1. a patient survey advertised through our website and our email list. There were 3 submissions from people either living with hepatitis C or affected by hepatitis C. All are from British Columbia: two males and one female.
2. one of us who is a volunteer, who has actively staffed HCV+ phone and email support lines over the course of several years and therefore has an in-depth knowledge of patient concerns and experiences; both authors of this report are/have been patient-researchers who have been reading scholarly articles about HCV for many years (20+ in one case).
3. input from our monthly support meetings has also been included.

2.2 Impact of Condition on Patients

In the last several years HepCBC has completed over 15 hepatitis C drug submissions for both CADTH and BC PharmaCare, and has answered Questions 2.2, 2.3, and 2.4 as many times. To avoid re-inventing the wheel, we refer you to our more detailed answers in six recent submissions made in July, August and October of 2014, plus March (in which two separate submissions were made for two drugs from the same company) and September, 2015.

- http://hepcbc.ca/wp-content/uploads/2015/10/20150928_ombitasvir_paritaprevir_ritonavir_CADTH_redact.pdf
- http://hepcbc.ca/wp-content/uploads/2015/03/20150310_daclatasvir_DAKLINZA_CADTH_redact.pdf
- http://hepcbc.ca/wp-content/uploads/2015/03/20150310_asunaprevir_SUNPREVA_CADTH_redact.pdf
- http://hepcbc.ca/wp-content/uploads/2014/10/20141008_ledipasvir_sofosbuvir_HARVONI_CADTH_redact.pdf
- http://hepcbc.ca/wp-content/uploads/2014/10/20140826_HCV_GT1_TherapeuticReview_CADTH.pdf
- http://hepcbc.ca/wp-content/uploads/2014/10/20140711_sofosbuvir_SOVALDI_Pharmacare_redact.pdf

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

The first is a female, age 62 from British Columbia, infected with GT3a. She has been through treatment twice and relapsed each time. Her main symptom from hepatitis C is a lack of energy. She writes that:

> *"… although I'm self-employed, I have trouble keeping up with work. At times [I] have to leave and go rest it gets worse as time goes by. I'm afraid of not being able to work some day."*

She also mentions:

"The aches and pains" and "Never getting enough sleep."

However, she is not currently on any of the new therapies because she doesn't have enough liver damage to qualify for provincial coverage.

The second respondent is a 69 year old male, living in BC, with GT3, who has undergone a liver transplant. He has had three previous treatment attempts. He suffers from a lack of energy and stamina which forced retirement at age 59. He writes that he needs treatment "before his new liver is compromised." He speaks for many GT3 sufferers when he writes that:

> *"Having type 3 means there are limited options for treatment and [I] would welcome any new treatments."*
>
> and (particularly since he is a transplant recipient):
>
> *"We don't want to go through hell again with my new liver."*

2.3 Patients' Experiences With Current Therapy

See Section 2.2 above

In the section above we have included two responses, which refer to previous (unsuccessful) treatment. As we noted, these patients, both GT3, have undergone treatment with interferon/ribavirin several times and have been unsuccessful.

Our third respondent, whose experience is detailed in section 3.2, is a male, aged 66, who was infected with GT1a. He has had 5 treatment attempts, the latest with Harvoni, and he is now in the post EOT "waiting" period. He will learn in mid-December whether he has achieved SVR12.

2.4 Impact on Caregivers

See Section 2.2 above

As we have noted in previous reviews, patients and their caregivers look forward to treatment options that are not only much more effective than was previously the case, but also require far less support, both mental and physical, than that which is often needed during treatment with interferon-containing regimes. One of our patient respondents, the male referred to above, who has undergone a liver transplant commented that, for caregivers, caring for someone with advanced HCV disease is:

> *"Not a fun ride, [they must] must be on alert 24/7."*

This comment encapsulates a Hep C carer's reality: when caring for someone with advanced liver disease, it is a relentless, ongoing task.

Section 3 — Information about the Drug Being Reviewed

3.1 Information Gathering

The information was gathered in the same way as for previous submissions (section 2.1). An online patient survey; personal experiences of volunteers and staff; input from our monthly support meetings. In addition, although we are aware that CADTH has access to all published data, we have referred to some published information, in support of several of the points we make, particularly in the following sections.

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

a) Based on no experience using the drug:

HepCBC believes that there is still a gap in treatment options, not only for the less common genotypes in Canada, but those hard-to-treat populations (patients with HIV coinfection; severe kidney disease; those infected with GT3 with or without cirrhosis; those with GTs other than GT3 but with cirrhosis; 1st generational PI treatment failure, interferon/ribavirin failure). One of the significant strengths of Merck's combination is that in trials it has been shown to be highly effective, even in those with the challenging characteristics identified above. Moreover, the combination has been demonstrated to be effective across several genotypes, making it a very versatile treatment option for a significant number of patients, including those infected with multiple genotypes. It is also extremely encouraging that Merck's combination can be combined with Gilead's sofosbuvir, enabling SVR rates in excess of 91% for GT3 sufferers, even if those sufferers have cirrhosis. We note also that there have been some good results in the C SWIFT Trial where some GT1 and GT3 patients have been able to achieve SVR with only 8 weeks of treatment when the Merck combination was also combined with Gilead's sofosbuvir.

As we have mentioned in previous submissions, all oral combinations with their shorter treatment durations, a minimal pill burden and seemingly far fewer side effects than previous interferon-containing treatments, are likely to require far less clinical management, fewer hospital visits, less time off work, etc., for most patients, although those with more serious disease in particular will need very close monitoring.

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

We have one patient report of experience with this combination. Unfortunately, as we can see, the patient had to discontinue due to a pre-existing condition. However, his experience of the Merck combination was positive. He is a male, aged 66, with GT1a. He has had five treatment attempts. He will find out if his latest course of treatment (Harvoni) has been successful in mid-December. He had this to say about the Merck combination:

> *"I had to come off the Merck trial because of atrial fibrillation. It was working, though. I was down to 84 copies of the virus after only 10 days...I liked it. Harvoni was okay but was very hard on my blood pressure. I was still detectable at week 4 (64 copies) but undetectable at week 12. I felt really different at week 10.*
>
> *"If a person has other conditions (heart), then monitoring is ABSOLUTELY essential. But treatment for the Merck and the Gilead products was easy and didn't need a caregiver (I can't speak for those who are disabled and may require those services.) But compared to interferon, this was a walk in the park.*

"The clinical trial I was on with the Merck Combo was a breeze!!! I had some minor sides for about 2 days (feeling a bit strange) and then I felt better than I had in 30 years!!!! I don't think the Merck combo triggered my atrial fibrillation. I have a pre-existing condition, and I had had extended periods of being in atrial fibrillation previous to the trial."

OUR RECOMMENDATION: The approval of Merck's combo yields excellent SVR rates, even across challenging populations. Approval is recommended by HepCBC (however, with the caveats we outline after our recommendation). As we have written elsewhere repeatedly, it is important that as many DAAs as possible are approved once they have been demonstrated to be both effective and safe in clinical trials. Approval of multiple DAAs will:

- Increase price competitiveness. There is near universal agreement among healthcare providers, both in Canada and worldwide, that the price of these medications remains unacceptably high, serving nobody's interests except the pharmaceutical companies.
- Enable medical professionals to become more proficient in prescribing DAAs more widely, increasing knowledge about both effectiveness and side effects as they relate to "real world" populations (in addition to those carefully selected for clinical trials).
- Produce more "real world" data allowing medical professionals to become experienced at "mixing and matching" DAAs to tailor treatments according to individual patient characteristics.
- Increase knowledge about side effects. In an "ideal world" any HCV drug regime would be completely free of side effects. However, this is never the case. While it is necessary to restrict access and to choose trial participants carefully for safety reasons, once a drug is approved and used more widely, additional concerns (contraindications, side effects) may come to light. All the approved third generation DAAs are highly effective, but their contraindications and side effects vary. We have to be prepared for additional side effects to surface as more people are treated. Although contraindications of which we may not be aware could arise, we believe, from what is known so far, that the trial data for Merck's combination supports high cure rates and a good safety profile.

In summary, Merck's all oral pan-genotypic treatment combination has impressive SVR rates of 95+% across a range of genotypes. It has also been shown to be effective in a range of challenging patient populations (including HIV co-infection, cirrhosis, advanced kidney disease, 1st generation DAA failure, prior treatment relapse and infection with G3). We have also seen that the combo can be combined with sofosbuvir and provide cure rates of 95%, even in patients with G3, and even those with cirrhosis. Its versatility and effectiveness make it a good candidate for a positive assessment by CADTH.

It should be noted that we have the following caveats to our recommendation:

- If approved, prescribers should familiarize themselves with those for whom the combination was less successful in trials. Overall failure rates in the C Edge trial were 4%. All those who failed treatment had a high baseline viral load (i.e., greater than 800,000 IU/ML) and/or had certain G1a baseline RAVs which caused a greater than 5 fold reduction in potency to elbasvir. Specialists should therefore be educated as to the specific characteristics associated with possible failure with grazoprevir/elbasvir. It will be necessary to select alternative drug combinations for patients with these characteristics, especially those with G1a baseline RAVs which reduce susceptibility so significantly to Merck's combo.
- HepCBC has noted the FDA announcement about Abbvie's Viekira Pak/Technivie, warning of the possibility of serious liver injury in some patients with advanced liver disease. If the Merck combination currently under review is approved, we support stringent monitoring, reporting and evaluation of side effects until such time as it can be established that treatment with

grazoprevir/elbasvir is safe for the most vulnerable hepatitis C patients. We acknowledge that it may be that greater numbers of patients need to be treated (in the "real world") than is possible in clinical trials to ascertain precisely the categories of patients for which this treatment is determined to be safe or to be less safe.

Section 4 — Additional Information

Subject to the points in the paragraph immediately above, HepCBC recommends approval of the Merck combination. As we have detailed in prior reviews, we remain concerned about the exorbitant price of the new DAAs generally. Our concern is that these prices will result in ever more stringent treatment criteria in order to reduce the numbers of patients eligible to be covered by provincial/territorial drug plans. Being treated before a patient's liver has deteriorated significantly means a greater chance of treatment success, together with the avoidance of other diseases, whether directly hepatic or caused indirectly by hepatitis C. Moreover, the recent FDA warning about the AbbVie drugs makes it all the more compelling to treat before patients reach a stage of liver disease where they can no longer safely be prescribed treatment.

HepCBC supports the need for urgently treating those who are most in danger from hepatitis C (before they can no longer be safely treated). We accept that some patients with milder liver damage may have to play the waiting game for one or two years more. However, we strongly support treatment for all those who are HCV RNA positive, whatever their liver disease stage, after prioritised patients have been given the opportunity of a cure. In addition, we emphasize our opposition to the "F2 criteria" as an eligibility factor for treatment, while at the same time recognising that those who exceed this threshold are the most urgently in need of treatment.

A related point is that we believe provincial governments must work together, rather than negotiate separately, to achieve fairer pricing throughout Canada for the new DAAs. There needs to be a co-ordinated, Canada-wide effort to ensure that the drugs are priced reasonably so that they are accessible wherever a sufferer lives.

The following sources provided material and references for this patient input review:
C-EDGE TN: PHASE 3 STUDY OF A 12-WEEK ORAL REGIMEN OF GRAZOPREVIR (GZR, MK-5172)/ELBASVIR (EBR, MK -8742) IN PATIENTS WITH CHRONIC HCV GENOTYPE (GT) 1, 4, OR 6 INFECTION
http://www.natap.org/2015/EASL/EASL_29.htm

C-EDGE **COINFECTION:** PHASE 3 STUDY OF GRAZOPREVIR/ELBASVIR IN PATIENTS WITH HCV/HIV (GT 1, 4, 6) http://www.natap.org/2015/EASL/EASL_07.htm

C-EDGE TE: Phase 3 EFFICACY AND SAFETY OF GRAZOPREVIR/ELBASVIR +/---RBV FOR 12 OR 16 WEEKS IN PATIENTS WITH HCV G1, G4 OR G6 INFECTION WHO PREVIOUSLY FAILED PEGINTERFERON/RBV
http://www.natap.org/2015/EASL/EASL_04.htm

C-SURFER: Phase 3 GRAZOPREVIR PLUS ELBASVIR IN TREATMENT-NAÏVE AND TREATMENT-EXPERIENCED PATIENTS WITH HEPATITIS C VIRUS GENOTYPE 1 INFECTION AND CHRONIC KIDNEY DISEASE
http://www.natap.org/2015/EASL/EASL_10.htm

C-SALVAGE: Phase 2 GRAZOPREVIR (GZR; MK-5172), ELBASVIR (EBR; MK-8742) AND RIBAVIRIN (RBV) FOR CHRONIC HCV-GENOTYPE 1 (GT1) INFECTION AFTER FAILURE OF DIRECT-ACTING ANTIVIRAL (DAA) THERAPY http://www.natap.org/2015/EASL/EASL_03.htm

C-SWIFT: GRAZOPREVIR/ELBASVIR + SOFOSBUVIR IN CIRRHOTIC AND NONCIRRHOTIC, TREATMENT-NAÏVE PATIENTS WITH HEPATITIS C VIRUS GENOTYPE 1 INFECTION, FOR DURATIONS OF 4, 6 OR 8 WEEKS AND GENOTYPE 3 INFECTION FOR DURATIONS OF 8 OR 12 WEEKS http://www.natap.org/2015/EASL/EASL_11.htm

C-Worthy: Phase 2 EFFICACY OF AN 8-WEEK REGIMEN OF GRAZOPREVIR PLUS ELBASVIR WITH AND WITHOUT RIBAVIRIN IN TREATMENT-NAIVE, NONCIRRHOTIC HCV GENOTYPE 1B INFECTION http://www.natap.org/2015/EASL/EASL_62.htm

FDA Drug Safety Communication: FDA WARNS OF SERIOUS LIVER INJURY RISK WITH HEPATITIS C TREATMENTS VIEKIRA PAK AND http://www.fda.gov/Drugs/DrugSafety/ucm468634.htm [accessed on October, 23, 2015]

We would also like to record our grateful thanks to those patients who responded to our request for input for this drug review.

Pacific Hepatitis C Network

Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest		**Grazoprevir/elbasvir**
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

1.1 Submitting Organization

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

1.2 Conflict of Interest Declarations

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

PHCN has received one-time project grants from AbbVie Corporation, Bristol-Myers Squibb, Gilead Science, Janssen Pharmaceuticals, and Merck Canada for the "Hepatitis C Treatment Information Project" (http://www.pacifichepc.org/hepctip/), 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 October 22 to November 4, 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 wellbeing. Invitations to complete the survey were sent out by word of mouth, through our mailing lists, and by posting the survey's information on our website and Facebook page. We received 15 completed surveys.

2.2 Impact of Condition on Patients

Our members have described hep C as a disease that kills slowly by degrees, a disease that is able to affect all aspects of life before it takes it.

Hepatitis C (HCV) is a serious and potentially life-threatening liver disease. It may lead to liver cirrhosis, cancer, liver failure, and even death. However, in many cases those life-threatening HCV developments only occur after patients spend time, sometimes years, worrying, rearranging their lives around HCV symptoms, and dealing with the psychological toll of having a communicable disease that many people fear and have misconceptions about.

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 affecting one's daily life. For example:

> "…my whole life, constantly aware of physical and mental capabilities. I could hardly walk a block without having to rest. Abdominal swelling prevented me from sleeping on my right side. My family has had to watch me die by degrees. Brain fog made me feel like I didn't matter. I was very prepared to die. I turned into an agoraphobic; worrying and not wanting to leave the house. My immune system depleted. I didn't want to be around other people who were sick. Always aware of the places I may get sick. I felt a complete loss of hope."

"Brain fog", a hep C symptom mentioned above, is a common symptom of hep C. The experience of "brain fog" includes difficulty thinking, remembering, understanding, and focusing. It 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.

In addition, 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."

Furthermore, the above quote not only touches on "brain fog", but it also expresses the uncertainty, loss of hope, helplessness, and worry, that often surrounds hep C. Hep C 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 due, in part, to the fact that it is a disease that one often has to wait and get sicker before receiving treatment, but, at the same time, is a disease that patients may get irreversibly sicker or die of before they find a treatment able to treat 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 a social isolation, which often comes from suffering fatigue, other hep C symptoms, the worry of passing HCV on, and/or 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.” Another recalled sharing her diagnosis with coworkers in confidence and having them turn around and share the news to the entire office. As a result, some of her coworkers switched jobs saying that they needed to protect their families. This is extremely damaging, as 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

For years the standard of care for HCV was pegylated interferon with ribavirin alone (for those with genotype 2-6 hep C) or with either telaprevir or boceprevir (for those with genotype 1). Sometimes these treatments were successful against the virus and caused only mild side effects. Sometimes their side effects were mild enough that patients were able to continue working and enjoying their lifestyles. However, in most cases, these treatments caused side effects that interrupted abilities to function normally and caused others, who hadn’t started treatment, to delay treatment or, at least, seriously wonder about delaying treatment.

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

In addition, some patients find the pill burden of taking multiple medications, possibly several times daily, both physically and mentally challenging. Organizing one’s daily schedule around medication times can be overwhelming.

Lastly, some of our members (with genotype 1 hep C) have been treated or are being treated with the new 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. They report that the treatments, such as Harvoni, cured them with little or no side effects. Others reported that they relapsed after taking the DAA and are now looking for other options.

2.4 Impact on Caregivers

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

In addition, 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 and their social network 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.

Furthermore, one of the most difficult situations for caregivers is when treatment has failed and their loved one is still ill, or if treatment isn't an option. A caregiver, for example, shared that when her husband was diagnosed, "the doctors just said to get his affairs in order." Caregivers want new treatments that can treat patients who weren't cured by treatments already available so that there is less of a chance that they will face the above.

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

Section 3 — Information about the Drug Being Reviewed

3.1 Information Gathering

Information was gathered through an online survey that was made available from October 22 to November 4, 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 wellbeing. Invitations to complete the survey were sent out by word of mouth, through our mailing lists, and by posting the survey's information on our website and Facebook page. We received 15 completed surveys.

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

a) Based on no experience using the drug:

Those with HCV have a couple of expectations for grazoprevir/elbasvir, however, the expectation that is foremost is that the treatment's high sustained virologic responses (SVRs) for those who are "hard to treat" will translate into a better chance of a cure for patients and, 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 grazoprevir/elbasvir 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 grazoprevir/elbasvir has also greatly improved treatment outcomes for those with compensated cirrhosis who are treatment-naive and treatment-experienced.

Grazoprevir/elbasvir 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 grazoprevir/elbasvir 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 grazoprevir/elbasvir, 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 grazoprevir/elbasvir 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 grazoprevir/elbasvir.

Section 4 — Additional Information

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

There is a want to get better, to improve their health, and to fully participate in all that they can dream of being involved in 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, such as grazoprevir/elbasvir, are coming and that these treatments will be available to them.

However, we are concerned that treatments, such as grazoprevir/elbasvir, that achieve different SVR rates for different population groups from approved treatments or hep C treatments currently ahead of grazoprevir/elbasvir 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 lower cure rates that are combined with pegylated interferon with/or ribavirin before having access to drugs like grazoprevir/elbasvir.

Lastly, along with individual lives possibly being saved and improved dramatically, early eligibility for and completion of treatments with high success rates, such as grazoprevir/elbasvir, 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.