Patient Group Input to CADTH

Canadian Treatment Action Council

Section 1 — General Information	
Name of the therapeutic review	Drugs for Chronic Hepatitis C Virus Infection
Name of patient group	Canadian Treatment Action Council (CTAC)
Patient group's contact information:	Canadian Treatment Action Council (CTAC) 555 Richmond St. W., Suite 612, Toronto (416) 410-6538 info@ctac.ca http://www.ctac.ca
Date of submission:	January 13, 2014

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 or hepatitis C.

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. Note: Only Full Individual and Organizational members have voting rights within the organization. CTAC recently incorporated hepatitis C in our organizational mandate (beyond HIV/HCV co-infection) and as such, is reviewing ways of including people living with hepatitis C as well as relevant organizations within our membership categories.

At the time of this writing, we have 463 full individual members, 125 full organizational members, 164 associate individual members and 43 associate organizational members, for a total of 795 members.

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 2012-2013 fiscal year: Abbott/AbbVie, Boehringer Ingelheim, Gilead Sciences, Janssen, MAC AIDS Foundation, and ViiV Healthcare.

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

None.

Section 2 — Condition and Current Therapy Information

2.1 Information Gathering

The information in this section is compiled from two recent patient input submissions CTAC prepared on simeprevir (Galexos, Janssen) and sofosbuvir (Sovaldi, Gilead). These submissions were informed by two patient surveys disseminated to attendees of national informational webinars on the expected clinical benefits of both medications. Additionally, this current submission is informed by hepatitis C epidemiological monitoring conducted by the Public Health Agency of Canada, as well as ongoing monitoring of registrational trials and published phase III results on these and additional emerging medications. A full description of the surveys referred to here as well as a list of publication citations consulted by CTAC on an ongoing basis is available upon request.

2.2 Impact of Condition on Patients1

Hepatitis C is a serious, often life-threatening virus that over time impairs liver function and, in some cases, causes decompensated cirrhosis and liver cancer. According to 2007 data from the Public Health Agency of Canada, approximately 242 521 Canadians are living with hepatitis C, with an estimated incidence of 7 945 new cases annually. Transmitted by blood-to-blood contact, hepatitis C is highly prevalent amongst people who do or have previously used injection drugs, with an estimated hepatitis C rate of 62.2% among all Canadians who use injection drugs, and 47.6% prevalence rate among Canadians who formerly used injection drugs. Due to inadequate screening of the blood supply in the 1980s, approximately 25 905 Canadians acquired hepatitis C from blood transfusions.

Although approximately 20% of people who acquire hepatitis C clear the virus on their own, 80% of people develop chronic hepatitis C which, over many years, can cause significant liver fibrosis and even cirrhosis. For many, the effects of hepatitis C can be mitigated with a healthy diet and exercise as well as reducing or eliminating alcohol intake. While it was previously thought that many people living with hepatitis C would not progress to have liver fibrosis necessitating treatment (generally understood as a Medvir score above F2), recent evidence suggests up to 64% of people will develop fibrosis progression to the point where treatment is necessary, with the goal of achieving a sustained virological response (SVR) or functional cure (Boccato et al. 2006). If untreated, over the longer term, it is estimated that 10-20% of people living with

chronic hepatitis C experience severe decompensated cirrhosis, and 1-4% are expected to develop liver cancer, requiring liver transplantation. According to the Ontario Burden of Infectious Disease Study, hepatitis C is the infectious disease responsible for the highest number of years of life lost due to premature mortality in health-adjusted life years.

Hepatitis C is often called a "silent killer" because it presents limited, if any, side effects throughout the course of infection. As respondent to a previous survey explained, "*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.*" Like this survey participant, many people are not tested until they have been living with chronic hepatitis C for a long time and are beginning to experience adverse events and a decline in quality of life as a result of advanced liver damage. The survey participant went on to say, "*I was diagnosed with F3 liver damage, so it is reasonable to say that hepatitis C treatment saved my life.*"

Another respondent, who continues to live with hepatitis C as s/he was a non-responder to previous treatment, experiences pervasive fatigue, noting s/he is "*functioning at half of usual level… I can walk but not jog; can only work out every second day. Exhausted most of the time. I have to plan how I spend my energy*."

A substantial number of people living with hepatitis C in Canada are also co-infected with HIV (10 458 of the 242 521 Canadians living with hepatitis C, or 0.43%). While it is less understood how hepatitis C affects a person's HIV disease progression, it is well established that HIV speeds up hepatitis C disease progression, with significant liver fibrosis and cirrhosis occurring within 10-15 years for people living with HIV/HCV co-infection (unlike 25-40 years for people living with hepatitis C alone). Consequently, the vast majority of people living with HIV/HCV co-infection urgently require hepatitis C treatment shortly after diagnosis to reduce the likelihood of life-threatening liver damage. To this end, one respondent expressed an increase in "*psychological anxiety about my new HCV and co-infection status that I had to deal with… in particular, concerns about the efficacy and side effects of treatment.*"

2.3 Patients' Experiences With Current Therapy

In late 2011, following a decade without advances in the previous standard of care (daily doses of ribavirin and weekly injections of pegylated interferon for 48 weeks), two new direct-acting antivirals of the protease inhibitor class, boceprevir (Victrelis, Merck) and telaprevir (Incivek, Vertex), were approved by Health Canada and recommended to public pharmaceutical coverage plans by the Common Drug Review to be added to ribavirin and pegylated interferon when treating people with hepatitis C genotype 1. While the addition of boceprevir and telaprevir substantially increased treatment efficacy in clinical trials (79% SVR rates for people treated with a telaprevir-based regimen and 66% SVR rates for boceprevir (ADVANCE and SPRINT-2 trials), recent, real-life data has suggested using boceprevir and telaprevir, especially for prior relapsers and null responders with advanced liver fibrosis and/or cirrhosis, is much less effective. Data reported in the French CUPIC cohort indicates 40% SVR rates for telaprevir and 41% SVR rates for boceprevir.

The addition of boceprevir and telaprevir to treatment regimens has dramatically exacerbated already highly intolerable adverse events associated with pegylated interferon and ribavirin. In 2012, a black box warning was added to telaprevir's label, notifying of severe rash-related fatalities. Boceprevir produced severe anemia, requiring multiple blood transfusions throughout treatment. Both of these significant

adverse events have been experienced among CTAC members who have undergone boceprevir or telaprevir-based treatments.

While none of our previous survey respondents had undertaken boceprevir or telaprevir-based treatments, all reported significant adverse events associated with the pegylated interferon and ribavirin components of their treatment. These significant adverse events included: fatigue, rash, itchiness, indigestion, mental health effects (especially clinical depression), hypoglyemia-like symptoms, cramping and dehydration. One respondent noted: "*The depression was the most difficult, but fatigue was cumulative over time and after 24 weeks I found I was missing work quite often.*" Another respondent described their side effects as "*weakness, worse than flu… Could not function more than 30% of the day. I ended up in ICU with pneumonia. I felt I was going to die*."

Two caregivers who responded to the previous surveys cited treatment cost and regional availability of liver clinic services as major inhibitors to treatment access. One respondent said: "*[People I work with] cannot access treatment. My region encompasses a very large area which is mostly rural. We have one liver clinic which only takes a handful of people every year.*" One respondent to a previous survey agreed, noting, "*I regularly met people at the clinic who had to travel long distances for their treatment in Toronto, from Northern Ontario, and people who needed grants or other support to pay for their treatment. These hardships are much tougher for people who are experiencing the side effects of hepatitis C treatment.*" Another previous survey respondent noted challenges in being referred to appropriate support groups and resources: "*I wanted to join a support group, but the service providers did not know where to refer me to.*"

Among people living with hepatitis C in Canada, uptake of currently available treatment has been extremely limited. While the Public Health Agency of Canada's epidemiological data suggests a significant proportion of people living with hepatitis C have been diagnosed (221 198 of 242 521 of Canadians estimated to be living with hepatitis C), recent IMS MIDAS data and publicly reported sales on unit volumes of pegylated interferon suggest only about 10 000 Canadians have undertaken hepatitis C treatment. Comparing this paucity of treatment uptake with our increasing understanding that more and more people will require treatment to address life-threatening liver health outcomes, a substantial unmet need exists in hepatitis C treatment in Canada.

2.4 Impact on Caregivers

Because hepatitis C treatment is extremely arduous, causing people to feel chronic fatigue, mental health side effects and other serious adverse events for a period of 48 weeks, caregivers' lives are also affected by the current standard of care. The caregivers who participated in the previous surveys noted the following challenges associated with the current standard of care facing the people living with hepatitis C they support: adherence, multiple side effects/adverse events including fatigue, nausea, depression, adequate nutrition and food security, anorexia/weight loss, as well as treatment failure (and anxiety anticipating potential treatment failure).

Caregivers who responded to the previous surveys found it difficult to provide support to people undergoing hepatitis C treatment, especially in ways the social safety net is inadequate to meet the needs of people living with hepatitis C. One caregiver respondent to a previous survey stated, "*Treatment is difficult for those who have their social determinants of health met. It is almost impossible for those who don't.*"

One respondent to a previous survey who had undergone hepatitis C treatment reported feeling like a burden to her/his family. The respondent noted: "*I was somewhat of a burden to my spouse during treatment as there were many regular activities I simply didn't have the energy to perform – household chores, repairs etc. and was often not up to socializing with other people.*" This relationship stress can certainly be mitigated by new medications that reduce treatment duration and minimize side effects.

Section 3 — Information about New Drugs

3.1 Information Gathering

The information presented here was gathered in the same manner as described in section 2.1, above.

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

In mid-2013, CTAC identified six unmet needs in currently available hepatitis C treatment: a) Increased SVR-related treatment outcomes; b) Shortened treatment duration; c) Minimized adverse events; d) Lowered pill burden; e) Interferon-free treatment; f) And ultimately, an effective cure for all people living with hepatitis C.

The three new medications under analysis in this therapeutic review achieve some of these six needs in comparison to currently available therapy in the following ways:

1. Simeprevir, sofosbuvir and faldaprevir should be listed because they are more effective and more tolerable than currently marketed DAAs: While boceprevir and telaprevir have successfully increased SVR rates amongst the Canadian patient population, they come with increased serious adverse events, and in real-life, harder-to-treat settings (as measured in the CUPIC cohort), are only moderately effective (see 2.2 above).

Sofosbuvir is projected to be approved for a 12-week treatment duration for people living with hepatitis C genotype 1, while registrational trials showed simeprevir and faldaprevir to be effective in most patients after 24 weeks of therapy. Additionally, each of these three medications do not show significant adverse events, and registrational trials indicated that adverse events experienced during therapy are more or less consistent with those experienced by people taking pegylated interferon and ribavirin alone.

Because of this, sofosbuvir, simeprevir and faldaprevir are preferable regimens to boceprevir and telaprevir and should be prescribed accordingly.

2. Simeprevir, sofosbuvir and faldaprevir should each be recommended by the Common Drug Review because they show differential efficacy rates in different segments of the patient population: Reviewing reported results from registrational trials, simeprevir, sofosbuvir and faldaprevir (combined with pegylated interferon and ribavirin) show varied efficacy rates in different aspects of the patient population:

- **Sofosbuvir** allows for the most effective treatment with the shortest duration for people who are **treatment naive.**, Studies have yet to be concluded (and are not expected prior to NOC) for treatment experienced or HIV co-infected people.

- **Simeprevir** has been shown to be largely effective across the treatment-experienced population. Studies have yet to be concluded in the HIV co-infected population.
- **Faldaprevir** has concluded registrational trials in the HIV co-infected population, showing high SVR rates.

For these reasons, each medication should be recommended, particularly becausephysicians will require flexibility to ensure a wide variety of patients have access to the best available medical intervention.

3. It is strongly encouraged that simeprevir, sofosbuvir and faldaprevir be recommended in such a way that pricing and prescription limitations will not inhibit future uses or best current available use of therapy: The fact that hepatitis C treatments are evolving and that some patients may require different treatment durations than others presents a challenge for pricing on public drug plans. While outside the scope of this therapeutic review, registrational trials for sofosbuvir have indicated 16 weeks of treatment is preferred for treatment experienced people living with hepatitis C genotypes 2 and 3. This means that the cost of sofosbuvir-based treatment for treatment experienced people living with genotypes 2 and 3 will be substantially higher if per unit pricing is consistent with a 12 week course of therapy.

Additionally, two phase 2 trials have shown promising results for sofosbuvir-based combinations in an interferon-free regimen, including one with simeprevir. In the sofosbuvir-simeprevir trial, both were prescribed with ribavirin to hepatitis C genotype 1 patients who were treatment naive and treatment experienced (including nulls). While the number of patients in the trial was quite small, SVR rates for this interferon-free combination ranged between 93-100%. Earlier in 2013, phase 2 results of a sofosbuvir-daclatasvir (BMS, expected 2014) combination showed 100% SVR rates.

These examples illustrate some regulatory and pricing challenges that are associated with a rapidly evolving therapeutic environment. Over the next coming years, it may become increasingly evident that some of the medications before the Common Drug Review may be best prescribed in combinations not initially indicated at the point of marketing. This said, prices negotiated with drug plans based on the current context may make such combinations financially prohibitive, threatening patient access to these eventual best combinations. Although future uses likely lie outside the formal limits of this therapeutic review, recommendations will undoubtedly impact potential frameworks financing future effective combinations of therapies across manufacturers. As a result, this therapeutic review must address the possibility that pricing decisions made in 2014 may have harder-to-forecast consequences. A recommendation on pricing indices and subsequent negotiations would be an ideal outcome.

4. All new hepatitis C treatments must be recommended for use in patients at F1 or above, or at F0 when a person is a member of a community affected by high hepatitis C prevalence: Hepatitis C treatment must be made available to people with F1 liver damage (in comparison to current recommendations of F2 or above) for two reasons:

a) Recent publications have demonstrated increased treatment efficacy and less loss of health-related quality of life for people who receive earlier treatment. Over the longer term, people with significant liver scarring will experience poorer health outcomes and will require increased health system resources, even after achieving SVR.
b) From a population health perspective, in order to reduce ongoing incidence of hepatitis C infection amongst communities with high prevalence rates, it will be necessary to offer treatment to people living with hepatitis C even when not medically indicated by liver fibrosis scores (ie. for people with F0). If the goal of introducing new, highly effective hepatitis C medications into the Canadian health system is (as

it ought to be) to cure hepatitis C at a population level, expanded treatment uptake must be prioritized in communities deeply affected by hepatitis C.

5. All treatment experienced people living with hepatitis C must be offered the opportunity to repeat hepatitis C treatment with current or future direct-acting antivirals: CTAC asserts that "one-shot" approaches to hepatitis C treatment are not acceptable, considering the hepatitis C treatment pipeline is not as stagnant as it was in the late 1990s and early 2000s. With increasingly promising therapies are soon to be available, especially new combinations that may include medications currently being assessed by the Common Drug Review, imposing a limitation on treatment repetition at this juncture limits the abilities of people who could clear their hepatitis C infection with these new regimens, limiting long-term costs to the health system.

Section 4 — Additional Information

Not applicable.