Template for Submitting Patient Group Input to the Common Drug Review at CADTH

Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest		Sofosbuvir in combination with Velpatasvir
Name of the patient group		HepCBC Hepatitis C Education and Prevention Society
Name of the primary contact for this submission:		REDACT
Position or title with patient group		Board Member and HCV+ volunteer
Email		REDACT
Telephone number(s)		
Name of author (if different)		REDACT
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
Permission is granted to post this submission		X ☐ Yes ☐ No

CADTH will post this patient input submission on its website if permission is granted. See CDR Update — Issue 99 for details.

1.1 Submitting Organization

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

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

Both of the authors of this report have attended several educational conferences and meetings for which registration and travel expenses were funded by the pharmaceutical companies listed in (a).

Section 2 — Condition and Current Therapy Information

2.1 Information Gathering

(1) Data from patient surveys advertised through our website and our email list. Note that with each new DAA submission we have received fewer responses. We suspect patients are feeling overloaded with requests for such information from then and they no longer see a reason to keep telling us the same things.
(2) Data from volunteers and staff who have actively staffed HCV+ phone and email support lines over the course of several years and therefore have an in-depth knowledge of patient concerns and experiences.
(3) Both authors of this report are/have been patient-researchers who have been reading scholarly articles about HCV for many years (20+ in one case).

2.2 Impact of Condition on Patients

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

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

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

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

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

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

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

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

In this section, in addition to the above, we also include two responses to our request for patient input for a previous review. These patients, both GT3, have undergone treatment several times and have been unsuccessful. While the responses were gathered in connection with a review for another all-oral combination, they are nonetheless relevant to this one, because they reiterate the need for effective options for more difficult to treat populations (e.g. those with genotype 3).

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

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

She also mentions:
"The aches and pains" and "Never getting enough sleep."

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

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

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

2.3 Patients' Experiences With Current Therapy

Several all-oral treatments for HCV have been approved, both federally and provincially. However, these are not suitable for all patients. In our opinion, we need as many of the new DAAs approved as possible in order to increase prescribing flexibility, according to individual patient characteristics. Although less frequently, a few patients still fail the newer treatments. These patients need to have hope that one day their liver disease will be cured -- and without having to use the now-infamous drug, interferon, if possible. Approval of multiple DAAs reduces the likelihood of treatment failure, especially as additional data becomes available and doctors become more knowledgeable as they gain "real world" experience as to what combinations to prescribe. Those with genotype 3, those with advanced liver disease, prior treatment failure or coinfection (either with HBV or HIV) are examples of some groups for whom at least one (and ideally more than one) effective treatment option is still required. It is becoming more and more apparent that there is no "one size fits all" treatment, so approval of multiple DAAs which can be mixed and matched according to rapidly-changing research recommendations, is highly desirable.

Currently, the biggest barrier to treatment with the new DAA combinations is their high cost, which has led to insurers and governments rationing these cures. This is particularly frustrating for HCV patients, caregivers and doctors. Moreover, as liver disease advances, the risks are greatly increased, even following successful treatment (we comment on these points in later sections of this report). The cost factor means that those with less liver damage also suffer as they are not able to access treatment unless they have either very generous insurance plans or a lot of money.

2.4 Impact on Caregivers

As noted in previous reviews, patients and their caregivers have repeatedly expressed to us that they want treatment options with greatly improved efficacy than in previous interferon-based regimes. In addition, they look forward to treatments which are shorter and require far less support, both mental and physical, than was previously required. Of course, they want their family members to regain their ability to support their families, or at least not be a burden to them, as soon as possible.

Section 3 — Information about the Drug Being Reviewed

3.1 Information Gathering

The information was gathered in the same way as for previous submissions (section 2.1). One of our members also attended a CTAC webinar on the combination, where data from the Astral trials was discussed. In addition, although we are aware that CADTH has access to all published data, we have referred to some published information, in support of several of the points we make, particularly in the following sections.

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

a) *Based on no experience using the drug:*

Approval of the combination will increase treatment options adding to the all-oral regimes available. However, while HepCBC supports approval of the combination, our analysis of the data from the Astral trials, together with other emerging data from patients who have been treated with the new DAAs, HepCBC also notes that there are issues that need to be borne in mind, along with an approval.

The combination has been shown in the Astral trials to be highly effective globally across all seven genotypes, including difficult-to-treat populations such as those who have G3, those who have cirrhosis, and those who have previously failed treatment (including with DAAs). SVR12 rates are at around 97%+ including high rates for G3 (95%) and those with cirrhosis (even decompensated cirrhosis). The combination was compared in the Astral trials against SOF/RBV and clearly tops that alternative, especially for G3, where SOF/RBV is not a particularly effective option.
The combination has also been trialed among those with decompensated cirrhosis (Astral 4) and shown to be effective, especially with the inclusion of RBV. Whether to use RBV involves weighing the side effects of the drug in comparison to an increase in SVR for those with more advanced liver disease. The available data seems to indicate that RBV can be avoided by most people on this regime, although RBV addition may be considered in cases where advanced liver disease is a factor.

All-oral regimes are generally easier to tolerate than those containing interferon. Therefore, we anticipate fewer adverse events and less disruption to daily activities. Theoretically, there should be a reduction in hospital visits compared with the older, 1st or 2nd generation treatments. However, and as always, we support continued close monitoring of all patients undergoing any kind of HCV treatment regime. Although the new DAAs appear to have fewer side effects, as their use becomes more frequent, we expect more side effects and contraindications to emerge. This is inevitable as trials are generally conducted according to stringent eligibility criteria and may exclude or not capture certain populations.

Furthermore, we have noted the recent investigation by the EMA into the possibility of HBV reactivation among HCV patients taking the new interferon-free DAA treatments. Thus we believe that, until more information is available, patients who could be susceptible (i.e. those who have been previously infected with HBV, whether resolved or not) should be monitored closely and treatment modified appropriately. It is prudent to suggest that all HCV patients, about to embark on an all-oral regime, should have their HBV status confirmed prior to starting treatment, at least until the EMA investigation provides more data.

We also note that research has indicated a possible resurgence of liver cancer following (3rd generation) DAA treatment. While this is worrying, it also emphasizes the point that treatment of HCV patients before they present with advanced liver disease is essential to minimize the risk of

eventual HCC. HCC is a factor that must be considered carefully before a treatment regime is prescribed, at least until more data becomes available.

b) *Based on patients' experiences with the new drug as part of a clinical trial or through a manufacturer's compassionate supply:*
We do not have any patients in our group who have taken the combination. However, data from the Astral trials, which we discussed in a webinar run by CTAC, indicate not only high cure rates but fewer side effects amongst patients in the trials than in interferon-based therapy. The side effects appear to be on par with those experienced by patients on other all-oral HCV treatments. The main side effects seem to be fatigue, nausea and headache. However, if ribavirin needs to be included, ribavirin-induced side effects (e.g. anaemia, skin rashes, irritability etc.) should be expected.

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

The combination should be as easy to administer and to use as all the other approved 3rd generation DAAs (usually, one pill orally per day, unless ribavirin is included). In most cases, being cured of HCV will clearly benefit a patient in terms of their overall health. However, we must also draw attention to the current investigations into reactivation of HBV and resurgence of HCC in some populations. It may be the case that it is not always the optimum choice to treat every patient immediately without due consideration of adverse consequences which might arise as a result.

Section 4 — Additional Information

The points we have made in Section 3.2 above support:

- Approval of sofosbuvir in combination with velpatasvir, as it is a very versatile and effective treatment with high cure rates across all genotypes, even among those who are traditionally more difficult to treat.
- Close monitoring of all patients on HCV treatment is required, whatever the regime.
- That doctors and specialists should be mindful of contraindications and the importance of keeping abreast of emerging data on "real world" use.
- That HBV status and HCC history (if applicable) of an HCV patient needs to factored in to a decision on whether to treat, choice of treatment , and the monitoring regime to be applied both during and after treatment.
- That emerging data (especially in relation to treatment of HCV in those at high risk of HCC) continues to make a case for treating HCV patients before their liver disease is advanced.

References:

NATAP Conference reports

SOF/Velpatasvir, +GS-9857 - Sofosbuvir/Velpatasvir Fixed-Dose Combination for the Treatment of HCV in Patients With Decompensated Liver Disease: the Phase 3 ASTRAL-4 Study At URL: http://www.natap.org/2016/APASL/APASL_28.htm [accessed on 28 April, 2016]

NATAP Conference reports

High Efficacy of Sofosbuvir/Velpatasvir Across 7 HCV Genotypes and 46 Subtypes: Pooled Data From the ASTRAL1, 2 and 3 Trials at URL: http://www.natap.org/2015/hepDART/hepDART_08.htm [accessed on 28 April, 2016]

EMA reviews reviews direct-acting antivirals for hepatitis C: Review to investigate possible hepatitis B re-activation at URL: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Direct-acting_antivirals_for_hepatitis_C_20/Procedure_started/WC500203479.pdf [accessed on 16 April, 2016]

High rate of early cancer recurrence following direct-acting antiviral treatment for hep C virus at URL: http://www.eurekalert.org/pub_releases/2016-04/eaft-hro041316.php [accessed on 16 April, 2016]

With thanks to Adam Cook and CTAC for an opportunity to analyse the data from the Astral trials at the webinar on 2 May, 2016