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:	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 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-NAIVE 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-NAIVE 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.