BC Pharmacare HepCBC Submission regarding Merck's Zepatier™

1) Conf. of eligibility: YES

2) Patient Group Name & name of representative completing this questionnaire:

HepCBC Hepatitis C Education and Prevention Society.
Representative completing questionnaire: REDACTED

3) Organization's Address

#20-1139 Yates St.

4) City

Victoria, BC

5) Postal code

V8V-3N2

6) Conflict of Interest Y/N = Y

7) Describe conflict of interest

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, Boehringer-Ingelheim, and AbbVie. In addition, one of the co-authors of this report has attended several educational conferences and meetings for which registration and travel expenses were funded by the pharmaceutical companies listed above.

8) Read PharmaCare info sheet? YES

9) Describe how the condition or disease for which this drug is used affects the day-to-day life of patients in your group.

HepCBC: Chronic hepatitis C can affect the patient in a variety of ways. In many cases there are no obvious symptoms for many decades, while the virus is "silently" destroying the liver; or the symptoms may be mistaken for some other disease such as fibromyalgia or chronic fatigue. Those with undiagnosed hepatitis C are unaware that lifestyle changes could slow the progression of the disease, are unaware that treatment could stop its progression entirely, or that they are in danger of passing a serious disease to others. For others, the symptoms are much more obvious and debilitating. In these situations, doctors are more likely to pursue active testing/monitoring and suggest aggressive treatment.

Besides the physical symptoms, there are many hidden ways chronic hepatitis C affects sufferers' daily lives. One common manifestation of hepatitis C is depression. Depression kills relationships along with

joy, and “brain fog” (another common manifestation) stifles concentration and clarity, slowly progressing along the spectrum to encephalopathy. Many experience fear of future disability and inability to support self and family, and fear of losing relationships, housing, or job due to commonly-held stereotypes and stigma against those with hepatitis C, as the patient experiences below demonstrate:

Pt. 1:

Female, 69 years old
Last biopsy in 2010: stage 3 bridging fibrosis
No co-infections
Infected by a blood transfusion in 1955 (60 years ago)
Diagnosed in 1994 (21 years ago)
Genotypes 2 and 4
Treated with Interferon in 1995 – unsuccessfully:

“Hepatitis C has affected every aspect of most of my life. I suffer from constant fatigue and lack of stamina. This prevented me from following the teaching career I had prepared for and made employment next to impossible. Lack of employment has prevented me from preparing for my "retirement" years. I am charged double for travel insurance to visit family who live in USA. I have not been able to be as involved in my husband's, children's and grandchildren's lives as I would like to have been. I don't have the stamina to travel or even to get involved in community activities.”

Pt. 2:

Female, 63 years old: *“I have stage F3 liver damage. I was infected in 1982. I was diagnosed in June 2014 with genotype G1a. In May of this year I finished treatment with Harvoni and at the end of the treatment my viral load test indicated I was found to have ‘no virus detected’. During the last 30+ years I was unaware I was infected. Looking back I can see many of my symptoms, fatigue, memory problems, and muscle pains, were probably due at least in part to hep C. I always was looking for answers as to why I felt bad. When I was diagnosed last year it made my health situation understandable, and soon after starting Harvoni I experienced a sense of well-being which I hadn’t felt in a long time. The feeling of always having to ‘push’ to get through my day was gone.”*

Sufferers of hepatitis C report a variety of manifestations and symptoms of the disease. The most common that we regularly hear about from those afflicted who seek support, advice and guidance from our group, are listed below, starting with psycho-social effects and ending with those most potentially life-threatening. These manifestations cover a diverse range of effects, demonstrating that the consequences of hepatitis C for an individual can be devastating. Manifestations/symptoms can broadly be divided into two categories: physical and mental, although there is significant overlap between the two:

Psychological trauma of living with a stigmatised illness

Feeling “unclean” with anxieties over infecting others

Fear of or trauma from harsh interferon-based treatments

Fatigue

Depression

Frequently having to compensate, modify or avoid activities due to hepatitis C (both physical and social)

Thyroid problems

Stomach problems

Arthritis

Diabetes

Fibromyalgia

Ascites

Varices

Cirrhosis

Non-liver cancers

Liver cancer

Liver transplant

10) What drugs or other treatments have the patients in your group used, or are they currently using, for the condition or disease for which the drug under review would be used for?

Please list all of the drugs or other treatments and tell us about their experience with each. In particular, did they consider any of the drugs or treatments to be successful and why?)

HepCBC: patients in our group have undergone treatment for hepatitis C with a variety of drug combinations. Over the years, these combinations have ranged from interferon only, followed by peg-interferon plus ribavirin, or fairly recently (2011-2013), the dual combination of peg-interferon plus the addition of a 1st generation protease inhibitor (PI) - either boceprevir or telaprevir) or occasionally with a 2nd generation PI, simeprevir. Boceprevir and telaprevir are being phased out due as far superior drugs are not available, and peg-interferon use is generally confined (in combination with sofosbuvir +ribavirin) to those in which its use brings significantly greater efficacy, such as those with genotype 5, or previously-treated genotype 2/3 patients with cirrhosis.

Simeprevir, on the other hand, only requires one pill a day (either together with peg-interferon and ribavirin or it has sometimes been prescribed “off label” in combination with sofosbuvir). However, simeprevir has not been without its drawbacks as it is fairly ineffective for Genotype 1a sufferers who have the Q80K polymorphism (which can naturally occur in the hepatitis C virus and almost exclusively in genotype 1a), so those with the 1a subtype need to be tested before treatment starts. In February this year Health Canada reported a possible link between simeprevir and liver function impairment and recommends that patients with moderate to severe liver damage should not use simeprevir.

It would not be an understatement to say that the addition of the boceprevir or telaprevir resulted in two of the toughest treatments there have ever been (or ever will be) for hepatitis C, while not being particularly effective for many. The terrible side effects of Peg-INF, boceprevir, and telaprevir have given

hepatitis C treatment a bad reputation. However, we are learning this is no longer the case with the new generation of (mainly) interferon-free DAA regimes, such as Sovaldi™, Harvoni™, Holkira Pak™ and now, there is the possibility of Genotypes 1a, 1b, 3, and 4 being treated with Zepatier™ (elbasvir/grazoprevir).

Hepatitis C patients, especially those within our group, tend to be fairly knowledgeable and well-informed about their condition as well as current and possible future treatments. Many of them have either had to avoid (or wanted to avoid) treatments containing interferon and/or ribavirin and/or a 1st/2nd generation PI. A increasing number of our group has had access to interferon-free treatments, either in the context of a clinical trial or through new third generation DAA treatments (Sovaldi™, Harvoni, or Holkira Pak™) now covered by BC PharmaCare. We are starting to hear many more success stories as people are treated with the new, far easier to tolerate, DAAs. We publish the rapidly-growing list of Canadians who have celebrated "SVR 12" on our "HepCBC Honour Roll" every month.

Over the decades there have been many treatment failures, particularly on dual therapy (peg-INF/ribavirin), particularly amongst genotype 1 patients. This was before an understanding of how the variation in the IL28b (host) gene subtype increases or decreases the likelihood of interferon treatment success. In addition, peg-INF and ribavirin produce difficult side effects in most patients (e.g. influenza symptoms, anaemia sometimes leading to blood transfusions or even cardiac arrest, inability to work or care for oneself, etc.). Furthermore, and as previously noted, toxicity is significantly increased by the inclusion of one of the early PIs. Even more concerning is the fact that the effects of peg-INF treatment seem to continue for the majority of patients well after the end of treatment, even (in some cases) permanently. These include often serious and long lasting disorders (e.g., thyroid disorders, peripheral neuropathy, arthritis, etc.). Many patients, whether they achieve SVR or not, frequently report feeling worse than before treatment. By contrast, those from our group who have been fortunate enough to be treated or re-treated with interferon-free regimes (usually Harvoni or Holkira Pak) report far fewer side effects. To date, we have not heard of long-lasting consequences like those experienced following treatment with interferon, although we have noted the recently announced investigation by the EMA into HBV reactivation following DAA treatment, plus we have also noted that recent research has identified a possible link between DAA treatment and resurgence of HCC, and between DAA treatment of cirrhotics and rapid liver decompensation, as well as other serious adverse events (J.H. Hoofnagle, EASL Journal of Hepatology 2016, vol. 64).

11) If the patients in your group have tried the drug under review, please tell us about the effects they experienced.

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. This was the fourth of five treatment attempts. He later took Harvoni successfully, and has been SVR since December, 2015. 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. On Harvoni, 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."

12) How do you think the patients in your group could benefit from the drug under view? (For example: relief of existing symptoms; improvement in quality of life; or improvements to their condition and their long term health and well-being. Please provide details.)

OUR RECOMMENDATION: The approval of Merck's combo for genotypes 1, 3 and 4 should result in excellent SVR rates, even across challenging populations. Moreover, as it can be combined with Gilead's sofosbuvir for G3 patients (for whom there are currently fewer, effective all oral options), we believe it is vital to approve it. Combining Zepatier with Gilead's sofosbuvir, enables 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. Being free from the threat of complications arising from hepatitis C (cirrhosis, liver failure, liver cancer) and being free from the debilitating symptoms this disease causes will improve the quality of life. Zepatier will add to the list of effective treatments BC PhamaCare is able to offer patients.

13) Are there additional factors your organisation would like PhamaCare to consider during its review of this drug? (For example: does the drug meet any special patients needs that have not been met by other drugs or treatments? Is the drug easier to use than other drugs; does the drug reduce visits to the hospital; does the drug reduce days off work or school; or are the drug's side effects acceptable or tolerable?).

Approval is therefore recommended by HepCBC (although with the caveats we outline below). While treatments for hepatitis C with the new DAAs require close monitoring, side effects are minimal compared with older treatments. Patients undergoing treatment are far more likely to be able to continue work, study or go about their daily routine.

As HepCBC has written elsewhere and 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 (the example of the possibility of combining Zepatier™ with sofsobuvir for G3 patients highlights how the new DAAs may be combined).
- 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. Both the lack of cross-regime comparisons, and the lack of controls in most of the DAA trials have been noted as research weaknesses and gaps that widespread usage will enable researchers to address.

In summary, Merck's all oral pan-genotypic treatment combination has impressive SVR rates of 95+% across several 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 noted 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 worthwhile addition to the BCPharmaCare formulary.

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 Zepatier. 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 that with some of the new DAAs, there is the possibility of serious liver injury in 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 Zepatier 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.
- If approved, clinicians should ensure they are up to date with new guidelines as they become available in relation to treating HBV co-infected individuals with the new DAAs and in relation to data on HCC resurgence.

Subject to the points in the paragraph immediately above, HepCBC recommends approval of the Merck's Zepatier™. 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, and the greater number of quality-adjusted life years (QALY's) the average patient will attain. Successful treatment puts a stop to HCV-related liver damage and in most cases results in some degree of reversal of liver damage, preventing other hepatic and non-hepatic HCV complications. However, it is essential to treat before patients reach a stage of liver disease where they can no longer safely be prescribed treatment, and the earlier the treatment, the greater its positive effects.

HepCBC supports the need for urgently treating those 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:

Merck's Pivotal Phase 3 C-EDGE Program Evaluating Grazoprevir/Elbasvir Shows High Sustained Virologic Responses Across Broad Range of Patients with Chronic Hepatitis C Virus Infection at URL: http://www.mercknewsroom.com/news-release/hepatitis-c-newsroom/mercks-pivotal-phase-3-c-edge-program-evaluating-grazoprevirelbasv [accessed on April, 16, 2016]

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

Results from Merck's Phase 3 Study of Investigational Chronic Hepatitis C Therapy Elbasvir/Grazoprevir in Patients with Advanced Chronic Kidney Disease Published in The Lancet at URL: http://www.mercknewsroom.com/news-release/hepatitis-c-newsroom/results-mercks-phase-3-study-investigational-chronic-hepatitis-c-t accessed on April 16, 2016]

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: **C-SWIFT: Grazoprevir (MK-5172) + Elbasvir (MK-8742) + Sofosbuvir in Treatment-Naive Patients With Hepatitis C Virus Genotype 1 Infection, With and Without Cirrhosis, for Durations of 4, 6, or 8 Weeks (Interim Results)**
http://www.natap.org/2014/AASLD/AASLD_11.htm [accessed on April 16, 2016]

Final Results from the C-WORTHyStudy (Parts A and B) Presented at The Liver Meeting® and Published inThe Lancet at URL: http://www.mercknewsroom.com/news-release/hepatitis-c-newsroom/merck-announces-results-phase-2-study-investigational-chronic-he-0 [accessed on April 16, 2016]

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]

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 April 16, 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 April 16, 2016]