Patient Group General Questionnaire from HepCBC Hepatitis C Education and Prevention Society Submitted to BC PharmaCare November 10, 2017

Welcome to B.C. PharmaCare's Public Input Questionnaire for drugs being reviewed under the B.C. Drug Review Process.

This patient group questionnaire is for
glecaprevir in combination with pibrentasvir / Maviret™ for chronic hepatitis C.

Respondent information

Confirmation of Eligibility

1. I am a representative of a patient group that represents patients in British Columbia who have the medical condition or disease which the drug under review would be used for **AND**
The patient group which I represent has registered with PharmaCare to give input.*
For more information, visit patient group eligibility requirements.
YES

Contact Information

Your contact information will only be used to retrieve your submission if you submit a request under the Freedom of Information and Protection of Privacy Act (FOIPPA). It will not be used for any other purpose.

2. **First and Last name*** **Shakuntala Soden, PhD, Education Project Mgr. and Cheryl Reitz, MA, Volunteer**
3. **Home Street Address*** **#20-1139 Yates St.**
4. **City:** **Victoria**
5. **Postal Code:** **V8V 3N2**

Conflict of Interest Declaration

6. Does your patient group have any Conflicts of Interest to declare?* (If you answer "yes", please complete question 7, which will follow.)
YES

7. Describe any Conflicts of Interest below.*
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, Gilead Sciences, Janssen Pharmaceuticals, Bristol-Myers Squibb, and AbbVie, plus support from Rx&D, the pharmaceutical umbrella organization.

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 above

Questions on the drug under review

Question 8 is mandatory; all other questions in this section are optional.

8. Have you read the PharmaCare information sheet for this drug?*

(If you would like to read this information now, click on the "this drug's information sheet" link in the *What this drug is for* column of the List of Drugs Under Review. The information sheet will open in a new tab.)*

YES I HAVE READ THE INFORMATION SHEET

9. Describe how the medical condition or disease which the drug under review would be used for affects the day-to-day life of the 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. Many of those with undiagnosed hepatitis C are unaware that lifestyle changes could slow the progression of the disease, and that they are in danger of passing a serious disease to others. They are also unaware that treatment could stop its progression entirely. 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 other hidden ways chronic hepatitis C affects sufferers' daily lives. One common manifestation of hepatitis C is depression. Depression kills relationships along with joy. "Brain fog" (another common manifestation) stifles concentration and clarity, slowly progressing along the spectrum to hepatic encephalopathy (HE). Sufferers experience progressively debilitating symptoms others see only as personal failures. On top of this is fear of becoming a burden on family and friends as the patient experiences below demonstrate.

In this section, we include four responses to our request for patient input: one from a GT1 patient, one from a GT2b patient and two from GT3 patients.

The GT3 patients had both undergone treatment several times unsuccessfully. They reiterate the need for effective options for more difficult to treat populations such as theirs. We at HepCBC welcome the opportunity that any effective treatment would offer for GT3 patients, as well as for those infected with other genotypes.

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 70 year old male, living in British Columbia, with GT3, who underwent a liver transplant at age 66. He has had three previous unsuccessful 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."
Like many other patients, this man was infected via blood transfusion (in 1957 at age 10). He also writes:
"Treatment for GT3, post transplant has been hard to come by. [I] Hope it will relieve fatigue and other side effects".

The third response was from a GT2b female from the USA, age 63:
"Hep C drastically affected my life. It took about 25-30 years for me to start showing intense symptoms. I believe it took that long because I was not a drinker. But when the symptoms started it came on strong. I had intense body pain and overwhelming fatigue. I kept going to my doctor trying to get help. They had no idea what was going on; at one point I was accused of drug seeking. After about 6 months, I was having trouble at work. I worked at a major grocery store and

was required to work various shifts. I had trouble getting to work on time and (eventually) *was fired. The funny thing is, I was initially glad because I could stay in bed and sleep. But within 2 months I was unable to pay rent and lost my apartment. I tried to get unemployment* (compensation) *but couldn't because I was too sick and was unable to look or accept any job. Because the doctors still hadn't diagnosed me I had no proof of my illness. I ended up sleeping in my car. After about 8 months my brother paid for a motel room for me but he felt I was faking it. So he quit helping after a few months. I was in my car for another year and went to a homeless clinic to get pain medication and help. My pain all throughout my body was intense. They ran a bunch of tests and found out I had HepC. It took another 2 months before I was able to see a liver doctor. He confirmed it and told me there were medications that could cure me. But I wasn't sick enough."*

The fourth patient is a GT1 female from Ontario, age 68, now post-transplant:
"Over the years, I experienced fatigue a great deal, but there was nothing else causing problems that I knew of. I thought the fatigue was due to everything that I was doing – teaching and being an organist as well as doing my job as a wife and mother. I looked around at many friends and wondered why they weren't as tired as I was. No matter what, I couldn't stay up as late or do as much without getting overly tired. I figured it was just me. (Eventually…)*, my doctor called me into his office to tell me that he had noticed my blood platelets were going down.* (He referred her to an internist who told her…) *that my spleen was enlarged and that my liver was hard.* (But for over two years, no one followed up on this)*…I was having trouble eating some food. Fish, especially, made me throw up, so I stopped eating fish. I started being very careful about what I ate when we went out, being careful to avoid things that I thought might make me ill…I continued doing the things I usually did, including administrative work at the local music festival, but still felt fatigued a great deal of the time. I began to notice some little things happening. I saw white spots on my tongue. My Dr. sent me to an ENT, as he was concerned it was cancer. He looked at my tongue on the first visit, and set up a second visit to do a biopsy. When I went the second time, he decided that he didn't know what it was, but he didn't think it was serious. (I found out later that this was a symptom of liver disease, as was the fatigue). This was 2½ years after my first specialist. I think another six months to a year went by before I plucked up the courage to ask my doctor if my gallbladder could be causing my symptoms. I knew that throwing up after eating certain foods could be caused by gallbladder trouble, and I knew I did have some stones. The only thing was, I didn't have the pain that I thought was associated with gallbladder trouble. My right side was tender, though I thought it was from sleeping on my right side all the time. Fortunately for me, my doctor didn't question anything, and instead, asked which surgeon I'd like to see…As I waited in (the surgeon's) examining room, I knew the doctor was looking at things on the computer. When he came in to see me, almost the first thing he said to me was, "Have you ever had hepatitis?" My answer was, "Not that I know of." Off I went for blood work (almost everything on the page had been checked off* including Hepatitis A, B & C. He also sent me for a liver MRI…(She was told…) *I had hepatitis C, and it had damaged my liver."*

10. What drugs or other treatments have the patients in your group used, either now or in the past, to treat the medical condition or disease 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 a variety of treatments for hepatitis C. Over the years, HCV treatment ranged from interferon only, moving on to Pegylated-interferon (Peg-INF) plus ribavirin (side effects in most patients included influenza symptoms, anaemia, disruption of work, mood and behaviour changes, and others even more serious, including permanent thyroid disorders, peripheral neuropathy, autoimmune disorders and arthritis). There were many treatment failures, particularly on 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. Then, about five years ago (2011-2013), researchers presented the dual combination of Peg-INF + ribavirin plus the addition of a 1st generation protease inhibitor (PI) — either boceprevir or telaprevir — or occasionally a 2nd generation PI, simeprevir.

The addition of boceprevir or telaprevir resulted in two of the toughest treatments there ever have been (or ever will be) for hepatitis C, while not being particularly effective for many. The terrible side effects of Peg-INF, ribavirin, boceprevir, and/or telaprevir gave hepatitis C treatment a bad reputation. Boceprevir and telaprevir were phased out as far superior drugs became available, and Peg-INF 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. The side effects of ribavirin, still added to some treatments, seem to many patients to have become more tolerable as treatment time has significantly shortened, diminishing its cumulative effects. However,

ribavirin can exacerbate underlying heart disease.

Simeprevir, on the other hand, only requires one pill a day (either together with Peg-INF and ribavirin or as "off label" in combination with sofosbuvir). However, simeprevir has not been without its drawbacks, either, 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, 2016, Health Canada reported a possible link between simeprevir and liver function impairment, so it now recommends that patients with moderate to severe liver damage should not use simeprevir.

However, we are learning these kinds of problems are non-issues with the next generation of (mainly) interferon-free DAA regimes, such as Sovaldi™ (sofosbuvir), Harvoni™ (sofosbuvir+ledipasvir), Holkira Pak™(dasabuvir + ombitasvir/paritaprevir/ritonavir [+ ribavirin for GT 1a and cirrhotics]), Zepatier™ (elbasvir/grazoprevir), Epclusa™ (sofosbuvir+velpatasvir), and Sunvepra™ (asunaprevir)+Daklinza™ (daclatasvir). NOTE: Sovaldi™ is now only used occasionally, with added interferon and ribavirin for unusual GT1 cases or for GT2 or GT3; Holkira Pak™ is rarely prescribed; the Sunvepra™-Daklinza™ combo for GT1b is rarely prescribed; and a Daklinza™ +Sovaldi™ combo w/wo ribavirin is covered for GT3 only.

Those from our group who have been fortunate enough to be treated or re-treated with interferon-free regimes report far fewer side effects. To date, we have not heard of any consequences during or following treatment like those experienced following treatment with Peg-INF. However, we have noted the recently-announced investigation by the European Medicines Agency (EMA) into HBV reactivation following DAA treatment, plus a possible link reported between DAA treatment and resurgence of HCC, and another possible link between DAA treatment of cirrhotics and rapid liver decompensation (J.H. Hoofnagle, EASL *Journal of Hepatology* 2016, vol. 64).
Below is the experience of one of our Patient Group Members who tried five treatments before being cured. These are the treatments this patient tried and the effects caused by each of them:

Patient A had the following five treatments:
1. Interferon alone (unsuccessful) — Weight loss, flu-like symptoms, achiness, fatigue
2. Interferon + ribavirin (unsuccessful) — As above, but worse
3. Interferon low-dose maintenance (successful in keeping the disease from progressing but no permanent cure) — Slight fatigue/achiness
4. Peg-IFN + ribavirin (unsuccessful) — Weight loss, flu-like symptoms, achiness, fatigue, but less than #2 above.
5. Daclatasvir + asunaprevir (successful) — NO side effects.

And here is the experience of another typical patient in our group, who only needed one course of treatment, but that treatment was tough and challenging:

Patient B:
I was treated with Peg-INF, ribavirin and boceprevir in 2013. The treatment was successful and I am very grateful to be free of the threat from hepatitis C. However, it was an extremely tough 30 weeks: I could not have worked (luckily my family supported me). I spent days in bed. I was also terribly anaemic. In addition, it took me many months to recover following treatment. Although free of the disease, I still suffer lingering effects which I suspect are a result of the combination of drugs I took or of at least one of them. For example, one of my toes is numb. I also have extremely dry eyes.

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

We have input from one patient who was accepted into a clinical trial for this treatment combo. This patient is female, aged 63, Fibrosis F2 and had been infected for approximately 30 years with GT2b. The patient had previously been unable to avail herself of treatment with the new DAAs because her specialist concluded that she was not sick enough. This was in spite of numerous devastating physical and emotional side effects from the HCV virus including her inability to continue to work and the subsequent loss of her home. Her experience with the clinical trial:

"The first 3 months I was on a placebo but was given the actual drug in April of 2016. My viral load dropped to half after 2 weeks. At 6 weeks I wasn't registering any virus in my system. At 3 months at the end of treatment I was told it

looked like I was cured but wasn't 'officially' cured until my final blood test in Jan 2017. The only side effects I had were in the beginning I felt nausea. I was given some pills that took it away. No bad effects. It is hard to know if some of what I was feeling were side effects or effects from being ill with Hep. After I was treated my energy level went from 30% of normal to 80% of normal. I was able to stay awake for 4 or 5 hours at a time and was able to walk to store and bathe, etc. It slowly got better and I was able to do so much more.

Even though I was feeling quite sick and depressed when I was told I couldn't get treated through my insurance, it brought out this anger and determination to get treated. I couldn't believe that I was expected to get close to death before I would be worthy enough to get cured… I was the new reality. I also refused to suffer in silence. A few people I know were afraid to tell people they had Hep C. I ignored the stigma. I believe that allowing access to this drug will go a long way to getting rid of Hep C in our lifetime. It hurts me to know that so many had to continue to suffer because of not having the money to buy the drug. I don't know what else to say. It saved my life. Thank you for allowing me to participate. I am available any time if you need anymore."

12. How do you think the patients in your group could benefit from using the drug under review?

(For example: relief of existing symptoms; improvement in quality of life; or improvements to their condition and long-term health and well-being. Please provide details.)

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 trials, together with other emerging data from patients who have been treated with the new DAAs, requires us to note some issues that need to be carefully considered along with any approval.

The combination has been shown in the range of trials (for example: Expedition, Magellan, Endurance) to be highly effective globally across the main 6 genotypes, including difficult-to-treat populations such as those who have GT3, those who have cirrhosis, or those who have previously failed treatment (including with the new DAAs). A further positive result is that the combination appears to be both effective and safe even for those with renal disease. SVR12 (Sustained Viral Response after 12 weeks following end of therapy, in other words "Cure") rates are excellent at almost 100% for some populations, including high rates for those with the problematic GT3 (98%+), and those with cirrhosis. Furthermore, HIV co-infection did not affect cure rates and, in the majority of people, HIV therapy did not have to be interrupted. We note that the combination consists of a protease Inhibitor (NS3/4A) plus an NS5A inhibitor. For the small percentage of patients who have previously failed 3rd generation DAA therapy, glecaprevir/pibrentasvir offers an excellent chance for success which is extremely encouraging. Treatment duration is for either 8, 12 or 16 weeks, according to patient characteristics: to anyone who has taken an interferon based therapy for 48 weeks with its terrible side effects, this would seem to be a fantastically short duration!

All-oral regimes are generally easier to tolerate than those containing interferon. Nevertheless, there are some side effects with every HCV treatment, albeit that the side effects are much milder and less likely to interfere with a person's normal daily activities than those in interferon-based therapies. The main side effects seen with this combination are documented as: fatigue, headache, nausea and pruritus. We note a small percentage of Serious Adverse Events (SAEs) but are reassured by the trial data which evaluates these as being unrelated to the treatment medication. As ribavirin is not included, its problematic side effects need not be considered.

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 can expect more side effects, drug-drug interactions, contraindications, and possibly resistance to emerge with glecaprevir+pibrentasvir (as with any of the other DAAs). This is inevitable as trials are generally conducted according to stringent eligibility criteria and may exclude or not capture certain populations. They also do not, due to their nature, capture long-term data and thus do not show any long-term effects which might show up over time.

Furthermore, we have noted the recent and ongoing investigations 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. We believe that all HCV patients, considering HCV treatment with DAAs on an all-oral regime (i.e., no interferon), should have their HBV status confirmed prior to starting treatment. In this way, steps can be taken (e.g. the inclusion of anti HBV therapy) to minimize the risk of a potentially fatal HBV flare.

We also note that research has indicated a possible resurgence of liver cancer for a short period 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.

13. Are there any additional factors your organization would like PharmaCare to consider during its review of this drug? (For example: does the drug meet any special patient 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 intolerable?)

According to BC PharmaCare's Drug Information sheet for this combo, pricing may be a large factor in favour of this pan-genotypic regimen. Its cost per course of therapy is $44,667 to $89,333 depending on GT, cirrhosis status, and other factors determining length of treatment (8, 12- or 16 weeks). For GT 1 patients, this is competitive with Zepatier ($42,210 - $91,928). For all others (GT 2 > 6) the pricing is significantly below competing treatments, if given in the 8-week regimen. Prices are closer to those of competitors for 12 or 16-week regimens. For GT 3 in particular, its competitors are 2X to 3X more expensive.

HepCBC supports:

- Approval of glecaprevir in combination with pibrentasvir, 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 reflecting "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.
- The combination should be as easy to administer and to use as all the other approved 3rd generation DAAs. We note this particular combination means 3 pills taken once daily, but as no ribavirin needs be included, this should not pose problems for most people.
- Patients are more likely to be able to continue with their normal daily routines.
- In the overwhelming majority of cases, being cured of HCV will clearly benefit a patient in terms of their overall health (the exceptions to this might be patients with very advanced liver disease/history of HCC or those who suffer a serious, potentially life threatening, HBV flare).

References:

U.S. FDA Grants Priority Review to AbbVie for its Investigational Regimen of Glecaprevir/Pibrentasvir (G/P) for the Treatment of Chronic Hepatitis C in All Major Genotypes (GT1-6) http://www.prnewswire.com/news-releases/us-fda-grants-priority-review-to-abbvie-for-its-investigational-regimen-of-glecaprevirpibrentasvir-gp-for-the-treatment-of-chronic-hepatitis-c-in-all-major-genotypes-gt1-6-300401029.html [accessed on 2017-10-20]

Pharmacokinetics and Safety of Glecaprevir/Pibrentasvir in Adults With Chronic Genotype 1-6 Hepatitis C Virus Infection and Compensated Cirrhosis: An Integrated Analysis
http://www.natap.org/2017/EASL/EASL_10.htm [accessed on 2017-10-20]

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http://www.hepctip.ca/drug-pipeline-2/glecaprevir-pibrentasvir-granted-review/ [accessed on 2017-10-20]

EMA 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 2017-10-20]

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 2017-10-20]

BCPharmaCare Drug Information: glecaprevir-pibrentasvir at URL: https://www2.gov.bc.ca/assets/gov/health/health-drug-coverage/pharmacare/glecapevir-pibrentasvir-3540-info.pdf [accessed on 2017-10-31]

Conclusion

Thank you for your input to B.C. PharmaCare's review of this drug.

Your input, along with other information, will be considered in the drug review process.

Click the DONE button to submit your input and close this questionnaire.