August 19, 2015

BC Pharmacare HepCBC Submission regarding Daklinza™

1) Conf. of eligibility: YES

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

HepCBC Hepatitis C Education and Prevention Society.
Representatives completing questionnaire: Shakuntala Soden, PhD, Exec. Project Mgr. and Cheryl Reitz, MA, Board Secretary and Volunteer.

3) Organization's Address

#20-1139 Yates St. Victoria, BC

4) Postal code

V8V-3N2

5) Conflict of Interest Y/N = Y

6) 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.

7) Read PharmaCare info sheet? YES

8) 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 of lifestyle changes that 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, causing pain, negatively impacting patients' mobility, work, and/or family life. 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. There is the fear of losing relationships, housing, or job due to commonly-held stereotypes and stigma against those with hepatitis C. There is often fear that the toll of caring for a sick family member will drive care-giving relatives away. It can be a very socially-isolating disease. In addition, many relatives of hepatitis C sufferers experience loss and distress both emotionally and financially because of the disability or premature passing of a close family member.

Sufferers of hepatitis C report a variety of physical and mental manifestations of the disease. The most common among those who seek support, advice and guidance from our group, are listed below, in general order of severity. 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

Hopelessness and despair at being to eradicate the illness and to feel well ever again.

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

Thyroid problems

Stomach problems

Skin problems

Arthritis

Diabetes

Fibromyalgia

Ascites

Varices

Cirrhosis

Liver cancer

Liver transplant

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

HepCBC: We have two genotype 1B patients within our group who were treated with daclatasvir in combination with asunaprevir. They have this to say:

Patient 1: "I was cirrhotic and had brain fog so badly I had to close down my computer-based business. Then I took treatment with interferon+ribavirin for almost a year, with terrible side-effects, and it didn't work. A little over a year later, I took the daclatasvir/asunaprevir combo for 6 months. There were no side-effects; in fact I was able to walk the half-marathon mid-way through the treatment. And it worked…my cirrhosis has reversed (from 49.6 kPa at the start of the treatment to 18 kPa one year following treatment, and 14 kPa recently). I feel so much better and am able to look after my grandkids regularly. What a change!"

Patient 2: "I lived with the virus for over 40 years. I went through difficult treatment 4 times, and was crushed each time to hear it didn't work for me. The Daklinza/Sunpreva combo worked from the start--only 24 weeks and no side-effects. It makes me happy every time I think about it. "

Both these patients were fortunate enough to gain access to Daklinza in the context of a clinical trial. But we have no more patient reports to add to this submission because the drug is not yet approved, so few people have had access to it in BC.

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 this drug is used?

Please list all of the drugs and tell us about the experience of the patients in your group with each treatment.

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 (either boceprevir or telaprevir) or occasionally with a 2nd generation PI (simeprevir). These 1st and 2nd generation PI's (prior to the approval of sofosbuvir), have been limited to those with genotype 1; as well, they both compounded and increased the range of adverse effects of the interferon. During the time they were used as "Standard of Care", there were sometimes life-threatening events (e.g. severe anaemia, severe skin problems, low neutrophil counts, many drug/drug interactions etc.). These negative factors, together with an extremely high pill burden and very rigid dosing schedules, for both boceprevir and telaprevir, meant these treatments had a high drop-out rate. Other negative factors are that boceprevir and telaprevir have a low barrier to resistance, leading to the very real possibility, not only of treatment failure, but also to the emergence of resistant-associated variants, which may preclude future treatment options, at least for some time. Simeprevir only requires one pill a day plus peg-interferon and ribavirin. It has sometimes also been prescribed "off label" in combination with sofosbuvir. However, it should be noted that 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 comparison, we have found that patients who have taken the new generation of DAAs with their (mainly) interferon-free regimes have far superior cure rates, although, thus far, they have mainly been aimed at those with genotype 1. Indeed, those treatments approved by BC PharmaCare thus far fall into this group. Besides lots with 1A and 1B, we have patients with genotypes 2, 3, and 4 in our group. One

with genotype 2 was recently cured with standard-of-care, but a few months following treatment she developed liver cancer – we wonder if that could have been prevented if she had been able to get treated sooner? Another member with genotype 3 is cirrhotic, treatment-experienced, and unable to take interferon or ribavirin; he is hoping that a cure will be made available to him before he decompensates. And another, with genotype 4 who was cirrhotic just died recently while on Harvoni. During treatment, his cirrhosis became decompensated, finally he was removed from Harvoni, but then his kidneys - and soon thereafter his heart - failed. Harvoni was extremely hard on him, but if he'd been prescribed it sooner, he might have been able to withstand the side-effects and survive. We know of several other hepatitis C sufferers in this dire sort of situation, and they need help fast.

Over the decades we have seen countless treatment failures, particularly during dual therapy (peg-interferon/ribavirin), and 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-interferon and ribavirin produced debilitating side effects in most patients (e.g. influenza symptoms, extreme fatigue and nausea, anaemia sometimes requiring blood transfusions or even leading to cardiac arrest, inability to work or care for oneself, etc.). Furthermore, and as previously noted, toxicity was significantly increased by the inclusion of one of the early PIs.

We have also seen that the effects of interferon treatment continue for most patients well after the end of treatment, (in some cases, even permanently). These can include serious and long lasting disorders (e.g., thyroid disorders, peripheral neuropathy, arthritis, etc.). We've heard many patients report, whether they achieve SVR or not, feeling worse after treatment than they did before. In contrast, those from our group who have been fortunate enough to be treated or re-treated with interferon-free regimes report far fewer side effects. We believe this trend will continue as further new agents are added to the BC PharmaCare formulary and interferon / ribavirin is used less frequently, even for those with genotype 3 or genotype 4.

Hepatitis C patients, especially those within our group, tend to be fairly knowledgeable and well informed both about their condition, and about 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 $1^{st}/2^{nd}$ generation PI for the reasons noted above which have been well documented. By contrast, fewer sufferers have had access to interferon-free treatments, either in the context of a clinical trial or following approval (e.g. of Sovaldi™; Harvoni™; Holkira Pak™) by Health Canada and then by BC PharmaCare. Without doubt, these treatments have not only been far more effective, but they are also immeasurably easier to tolerate.

11) Please tell us why your organization believes this drug should be included in the BC PharmaCare program.

Let us start with the words of someone from our patient group:

Patient:
"If Sovaldi™ and Harvoni™ are going to be available to so few people through BC PharmaCare because of the high cost, something else that doesn't include Interferon has to be offered to those of us who have

been suffering for so many years and don't fall into Pharmacare's priorities (i.e., have an unusual combination of genotypes and a low risk of transmission to anyone else)."

Overall, HepCBC remains enthusiastic about the current new treatments that are being considered by BC PharmaCare. However, as we are all aware, there is by no means a perfect drug, or "one size fits all" solution which can be prescribed for all hepatitis C sufferers. Hepatitis C is a diverse and complex virus, and so we welcome the chance to approve several new agents, so that they can be prescribed in varying combinations. In this way, doctors will be able to "tailor" treatments and prescribe according to each patient's individual circumstances. For this reason, HepCBC would like to see the approval of Daklinza™ so it can be used in combination with other DAAs in tailored treatments, according to individual patient characteristics, including genotype.

We should remember that, contrary to previous thinking, genotype 3 has emerged as the most difficult genotype to treat, with characteristics such as more rapid disease progression and a tendency to other complexities such as "fatty liver". Having a range of effective drugs for doctors to choose from will no doubt assist in the treatment of this challenging population. We regard Daklinza™ as a highly significant and important drug which will help combat hepatitis C. In particular, the approval of Daklinza™ by BCPharmaCare should have a huge impact on the treatment of genotype 3 patients, who make up some 30.1% (1) of the patients who suffer from this disease worldwide. At the moment, they are not able to match the higher percentages of patients with genotype 1 (accounting for some 46.2% of HCV patients worldwide(1)) who are achieving SVR with the new treatments. Daklinza™, when combined with sofosbuvir (Sovalidi™) has been shown to be highly effective and to improve cure rates for patients with genotype 3. Genotype 3 is not only hard-to-treat but often a fast progressing genotype. The combination of Daklinza™ and sofosbuvir has recently been approved by the FDA for the treatment of those with genotype 3. (2)(3)

We should also remember that the focus of new treatments have not included genotype 4, at least not in a North American context. While the AbbVie combination with the same components as Holkira Pak minus dasabuvir (Viekirax®), Daklinza in combination with sofosbuvir would provide an effective option.

It should be noted, however, that Daklinza™ can be prescribed in other combinations apart from sofosbuvir. It is already approved in combination with asunaprevir in Japan for treatment of genotype 1 patients for whom an interferon containing regime is not suitable, including older patients and/or those with compensated cirrhosis. [(4)]. Furthermore, Daklinza™ is a pan-genotypic agent and has been included in the latest (2015) EASL recommendations as an alternative treatment, in combination with sofosbuvir, for genotypes 1, 2, 3, 4, 5 and 6, with or without ribavirin, according to disease characteristics (cirrhosis or non-cirrhosis) and treatment duration (cirrhotics may be treated for 24 weeks without ribavirin)(5). The fact that it is pan-genotypic and highly effective against genotype 3, means that, in our view, it is essential for BC PharmaCare to approve it.

Including Daklinza™ in the BC PharmaCare formulary will increase the options of being able to select the most effective drug combination for each individual patient, according to genotype and disease stage. In addition, although sufferers of genotype 4 comprise merely some 55,000 cases in North America (1.2% of the disease population in this region) [(5)], this is still a sizeable number of patients for whom treatment options are necessary. While numbers for genotypes 5 and 6 are even smaller in comparative terms (some 32,000 cases in North America)[(5)], this is not an insignificant number: these patients still deserve treatment. Approving Daklinza™ therefore "makes sense" because it may be prescribed (with

excellent results) along with sofosbuvir, whatever a patient's genotype, and with asunaprevir for genotype 1 specifically.

As we have indicated throughout this submission, whatever a patient's genotype, subtype, physical or disease characteristics, the costs of the new treatments present a considerable barrier to a cure. We therefore hope that BC will be successful in negotiating prices for the new agents, which enables treatment to be provided universally for all patients. Moreover, we believe that the more 'competitors' to Gilead's Sovaldi™ and Harvoni™ there are, that prices for all these effective new options will be (and should be) substantially reduced. While currently Holkira Pak™ is the highly effective "new kid on the hepatitis C treatment block", and presents an excellent alternative to Harvoni for some genotype 1 patients, it is not effective for genotype 3 sufferers. Daklinza™, on the other hand, can be given in combination with Sovaldi™ for this group, offering very good cure rates for this category of patient (and indeed for all the other genotypes).

As referred to above, we believe treatment should be available universally. Treatment is more successful the earlier it is initiated, but there is a current minimum threshold (throughout most of Canada including BC) of fibrosis level 2, which is determined by liver biopsy, Fibroscan, or other non-invasive means. However, by the time patients reach the F2 threshold, significant liver damage has already occurred. Once hepatitis C becomes chronic, it is almost never going to spontaneously go away. It can only get worse. Patients will suffer a reduced quality of life, and be more susceptible to serious diseases such as liver cancer. They are always at risk of inadvertently infecting others, especially if they are unaware that they have the disease.

There might have been a rationale for withholding treatment from those without advanced disease when only the less effective, older, harsher treatments were available (on a "treatment is worse than the disease" basis). However, this is far less relevant today, when there is the very realistic prospect that all patients can be cured quickly, and relatively easily as well. At the very least, we strongly argue for a greater percentage of patients to be treated than is currently the case. In order to make a significant impact on the prevalence of chronic hepatitis C and morbidity/mortality due to the disease, we suggest a minimum of 5%-6% per year, rather than the current 1.4%, which barely keeps up with the incidence of new cases.

Finally, equity issues resulting in treatment disparities (i.e., between urban or rural groups, or between those who have private insurance versus those who are completely dependent on BC PharmaCare) are beyond the scope of this review but something we hope will be investigated and addressed in the not too distant future.

To summarise, patients within our group are very excited about the new treatments, especially the interferon-free combinations. However, they are sometimes confused by the plethora of new drugs currently being tested in clinical trials/becoming available and their different classes. In addition, it should be emphasised that patients are almost always concerned and disappointed by the costs of these treatments and what this means for them (that they won't have access to them because of how expensive they are). This presents a very difficult situation: the cure is there, with no or few side effects and significantly reduced treatment durations. But the treatment is completely out of reach. HepCBC wants to encourage BC PharmaCare to continue to approve the new DAAs (in this case Daklinza™) as they become available and as they are shown to be highly effective as part of novel treatment options. Adding them to the formulary in this way gives the best chance of curing as many different types of

patient as possible, and will, we hope work towards a price reduction for all these remarkable drugs. Daklinza™ should be available, as Sovaldi™, Harvoni™ and Holkira Pak™ are now. In addition we should also move rapidly towards universal treatment of those infected with hepatitis C. We need to eradicate the unnecessary suffering that prolonged infection with this virus causes, now that effective cures are available, including for the harder to treat groups such as those infected with genotype 3 and for those for whom there are currently fewer treatment options such as those with infected with genotype 4 and indeed genotypes 5 and 6.

References

(1) Messina, J. P., Humphreys, I., Flaxman, A., Brown, A., Cooke, G. S., Pybus, O. G. and Barnes, E. (2015), Global distribution and prevalence of hepatitis C virus genotypes. Hepatology, 61: 77–87. doi: 10.1002/hep.27259

(2) Bristol-Myers, Introducing Daklinza Internet www page at URL: http://www.daklinza.bmscustomerconnect.com/ [accessed on August 18, 2015]

(3) FDA (July 24, 2015) 'FDA approves new treatment for chronic hepatitis C genotype 3 infections' internet WWW page at URL: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm455888.htm [accessed on August 4, 2015]

(4) Bristol Myers Squibb (July 7, 2014) 'Japan Approves First All-Oral, Interferon- and Ribavirin-Free Hepatitis C Treatment, Daklinza® (daclatasvir) and Sunvepra® (asunaprevir) Dual Regimen' internet WWW page at URL: http://news.bms.com/press-release/japan-approves-first-all-oral-interferon-and-ribavirin-free-hepatitis-c-treatment-dakl [accessed on August 4, 2015]

(5) European Association for the Study of the Liver (2015) 'EASL Recommendations on Treatment of Hepatitis C 2015' *Journal of Hepatology* Vol 63 pp199-236