Patient Group General Questionnaire from HepCBC Hepatitis C Education and Prevention Society Submitted to BC PharmaCare February 21, 2018

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
tenofovir alafenamide **/ Vemlidy™ for chronic hepatitis B.**

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***

REDACTED

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 viral hepatitis-oriented projects such as: Publishing educational materials, organizing educational forums, attending and presenting at educational conferences, advertising in newspapers (events and viral hepatitis 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.

A large number of people who are infected with HBV never have symptoms and may never realize they are infected, while unknowingly passing the disease on to family members, friends, and others. However, for those who do experience symptoms, these can be serious and deadly, impacting their lives physically, financially, emotionally, and socially.

ACUTE HEPATITIS B INFECTION: Possible symptoms of acute infection, which occurs with less than 10% of HBV-infected children and 30-50% of HBV-infected adults are: jaundice, fatigue, loss of appetite, nausea, and joint or abdominal pain. Acute infection is treated primarily by alleviating symptoms; there is no cure. This impacts patients severely but usually for a short time; some patients, however, die of liver failure during the acute phase.

CHRONIC HEPATITIS B (CHB) INFECTION: An estimated 420,000 persons are living with chronic hepatitis B (CHB) in Canada. Over time CHB may result in liver cirrhosis, liver cancer, decompensated liver disease and premature death. The risk of developing CHB is highest among those infected at birth (90%); risk decreases according to age at infection (as low as 5% in those who acquire HBV as older adults). Both prevalence and incidence of co-morbidities diabetes, hypertension, hyperlipidemia, renal impairment, chronic kidney disease, bone fracture, and osteoporosis increase in both CHB and non-CHB controls as income decreases and age increases. However, the presence of CHB, regardless of income or age, increases the risk of all of the above co-morbidities, particularly renal impairment and chronic kidney disease, in which the risk among those with CHB is about 2.5X that to those without CHB. HBV was the primary diagnosis for 4.2% of liver transplant recipients in Canada between 2005 and 2014.

IGNORANCE of risk factors and STIGMA against those with hepatitis B is still very strong, which can affect access to many important life opportunities such as employment, marriage and other sexual relationships, immigration, loans, and life insurance. This often encourages patients to refuse from disclosing, testing or undergoing treatments for HBV out of fear of social stigma and prejudice both for themselves and family members. There is frequently concern and shame among both patient and caregivers that others will assume the cause of the cirrhosis or death is due to "preventable" lifestyle issues such as alcohol abuse. When HBV is contracted through pregnancy, emotional distress can develop between the mother and the child due to a sense of guilt on the mother’s part or resentment on the child’s. Within immigrant families, there is sometimes fear that disclosing CHB can impact a family member’s legal or health insurance status.

It is important to note there are two completely different epidemics of hepatitis B in Canada. Age, lifestyle, risk factors, testing, education and support needs, and treatment can vary greatly among the two epidemics:

(1) Epidemic among “Prevalent” populations, primarily immigrants from HBV-endemic countries (mostly from Asia, Africa and the Middle East, Spain, Eastern Europe, and northern South America), their spouses who contracted the disease sexually and children who contracted the disease vertically. Those who contracted HBV through blood transfusion can also be considered “prevalent” as their risk of spreading the disease to others is limited. This is generally an older population with higher % of CHB.

(2) Epidemic among “Incident” (risk-based) populations such as IVDU, sex workers, current or former prisoners, and men who have sex with men (MSM). These are populations at high risk of both contracting HBV and passing it on to others. While it is generally a younger population with lower % of CHB, the population is aging and the need for CHB treatment will increase proportionately.

NOTE: Aboriginal-majority northern areas Alaska, Canada's North, and Greenland are both high-incidence and endemic areas so it's hard to know which category to put aboriginal people and residents of remote northern areas into. Really, it depends on each individual members' risk profile.

PREVALENT EPIDEMIC: Hepatitis B is on track to slowly disappear from the prevalent populations with the passing of the infected generations, as immunization will protect the younger generation, including intense therapy available as needed immediately after birth. CHB still severely affects current elders, however (estimated % of Cdn immigrants with CHB varies from 3% to almost 7%). We hope they will all be found and treated to enhance the quality and increase the length of their lives. Education and support of these people and their families, and availability of new treatments such as **tenofovir alafenamide** (also known as **tenofovir alafenamide fumarate** or **tenofovir alafenamide hemifumarate** or **TAF**) will be key. People in this population are sometimes confused with people in the incident population; as such they often suffer the same stigma associated with IVDU, prisoners, or sex workers.

INCIDENT EPIDEMIC: A hepatitis B epidemic continues to run through the incident populations; these people are at risk of both contracting and passing on the disease, but as they are generally younger than those in the prevalent populations, and not yet suffering symptoms, public health attention is more focused on providing them with harm reduction supplies and education than on treatment. In the early years of the disease, even if it has become CHB, there may be no symptoms and little interest in getting tested. Other problems may seem more acute in patients' lives such as housing, addiction, other (more acute) STDs, food security, stigma or prejudice, violence, abuse, and crime. It is generally once the patient has gotten older that CHB becomes a pressing issue, and the patient seeks treatment. Also sometimes considered among the at-risk 'incident' population are healthcare workers (from needle-stick injury), dialysis patients (from improperly sterilized equipment), and tattoo/piercing clients (from improperly sterilized or re-used equipment, ink, etc). However, these last three groups are not generally engaging in high-risk behaviours which would result in passing HBV to others (except possibly to family).

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?)

The treatments now in use include immunosuppressive therapy such as injected **interferon** for 48 weeks or less (rarely used now - for very mild CHB, or patients with compensated cirrhosis) and **lamivudine (LAM)** (no longer in preferred guidelines but still used by many). The current standard used throughout the world is generally a long term nucleos(t)ide oral therapy such as **entecavir (ETV)**, or **tenofovir disoproxil fumarate (TDF)**. It is widely accepted that ETV and TDF suppress HBV virus replication, prevent fibrosis progression, and can even reverse fibrosis, cirrhosis, and even decompensation; however, while reducing the risk of liver cancer, this risk is not eliminated. ETV and TDF are both effective and well-tolerated. The main problems are that (1) TDF has toxicity over long term use – it carries the risk of weakening the renal system and the bones and (2) resistance - it is high with LAM but very low with ETV (unless the person is already LAM-resistant). Resistance does not occur with TDF (a similar result is expected with TAF). The main downside to TDF seems to be the long-term damage to kidneys and bones. Lots of people are still taking ETV, and physicians we've heard from seem to think most current ETV and TDF patients will remain on their current treatment for now, if they're doing well.
*With both ETV and TDF, once creatinine clearance goes below 50 mL/min, the dosage must be reduced in order to prevent serious kidney/renal system damage..

11. If the patients in your group have tried the drug under review, please tell us about the effects they experienced.
We were not, unfortunately, able to find anyone to answer this question.

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.)

CHB patients hope that with proper medication, they will not get liver cancer, that their liver and kidneys will not fail, that they need not be in fear of accidentally passing on HBV, especially to their newborn babies or their spouse. They want to be able to provide for their families or at least not be a burden. They know there is not yet a cure, so they hope for suppression of the disease, its effects, and its virulence. They would prefer not to have to take treatment for extended periods, but realize in some cases that this will be necessary.

Given that Health Canada has issued a Notice of Compliance (June 19, 2017) and in the US the drug has FDA approval, patients and physicians seem to have a high degree of confidence in the medical value of TAF. TAF has been shown to be generally equivalent to the older drug TDF in efficacy in viral suppression, likelihood of becoming resistant, and safety. Total adverse events were the same (between 866 patients taking TAF and 432 patients taking TDF in a control group), and we were pleased to note that rates of HCC and death were lower in the TAF group.

Moreover, TAF is an improvement in two ways that we know of:
First, due to slight changes in the molecular structure, tenofovir alafenamide fumarate (TAF) is taken in by the blood much more efficiently than is tenofovir disoproxil fumarate (TDF). Thus, dosage of tenofovir can be reduced 90%. TAF's adult dosage (to patients with CHB and compensated liver disease) is only one 25 mg tablet per day. This contrasts to the 300 mg daily dosage for TDF. Because of the lower dosage of tenofovir, patients expect that they can take the medication TAF for extended periods with less potential for damage to their kidneys and bones. The indicators of renal safety (estimated glomerular filtration rates, serum creatine levels, and renal tubular function markers) as well as markers of bone degeneration show that TAF does significantly less damage to kidneys and bones than TDF through week 96. However, research into the long-term effects of TAF will continue into the future; patients likely expect that they will remain "guinea pigs" to some degree, but we predict they would be willing to accept this in return for the chance to prevent or lessen the long-term kidney and bone damage currently documented for long-term use of TDF. Related to this, patients with any kind of renal impairment now taking ETV or TDF require dose reduction when their creatinine clearance falls below 50 mL/minute. In contrast, no dose reduction is required for TAF until their creatinine clearance falls below 15 mL/minute, a significant advantage.

Second, for reasons not clearly understood, TAF seems to result in faster and greater normalization of ALT (indicator of ongoing liver damage) scores. Four different major studies have all shown this to be the case, with the difference in normalization rates averaging around 10% greater for TAF than TDF at the end of Week 96. Patients will likely be confused about what the best ALT upper limit of normal should be. Central Lab puts it at 43 for males and 35 for females. AASLD puts it at 30 for males and 19 for females. In all cases, however, this relationship (better normalization of ALT with TAF) holds. When using the Central Lab upper limit criteria, the relationship is more pronounced.

Downsides: The main downside of TAF will likely be its price. Patients must decide if the long-term benefits are worth the increased price this product will likely have for many years. Physicians we have talked to and heard (over Clinical Care Options webinars) suspect that the trend will be not to change to TAF as long as there is no obvious damage to kidneys or bones. This is too bad, considering that the use of TAF could well prevent such damage, adding significantly to QALYs preserved.
Pricing comparison**: TAF (Vemlidy)** is **$21.11** per day. This is compared to the hepatitis B treatments currently listed by BC PharmaCare below (prices courtesy CADTH Common Drug Review (CDR) Pharmacoeconomic Review Report for tenofovir alafenamide (Vemlidy)).

(1) **entecavir or ETV (generic),** especially for those with cirrhosis or portal hypertension, **$5.94** per day – CURRENT STANDARD OF CARE (1 of 2)
(2) **Viread™ or tenofovir disproxil [fumarate] or TDF (Gilead and generic)**, **$5.28** per day. Daily dose is 300 mg tenofovir (long-term use known to cause kidney and bone problems) – CURRENT STANDARD OF CARE (2 of 2)
(3) lamivudine (generic) **$3.81** per day. ***No longer in preferred guidelines but still used by many.***
(4) Intron A® or interferon alfa-2b injections are ***sometimes used on a temporary basis.*** Price varies with duration.
(5) adefovir dipivoxil (generic) for those with lamivudine resistance, **$20.27** per day. ***Very rarely used.***

TAF's product label has two "Serious Warnings and Precautions" for which physicians must monitor:
(1) lactic acidosis/severe hepatomegaly with steatosis during treatment, especially noted among females and the obese and (2) severe acute exacerbation of hepatitis B once treatment is stopped.

There are a few other possible safety concerns which may warrant further research, warnings and/or close monitoring, however. We had some concerns about significantly higher rates (in TAF patients vs. TDF patients) of lab abnormalities in fasting LDL cholesterol (6% vs. 1%), fasting glucose (1% vs. 0) and urine glucose (4% vs. 2%). So we'd like to see a recommendation that these factors in particular must be monitored closely in all TAF patients, at least until research shows it's unneeded.

Finally, the product monograph warns that "The safety and efficacy of VEMLIDY have not been established in patients co-infected with HIV-1 and HBV. HIV antibody testing should be offered to all HBV infected patients before initiating therapy with VEMLIDY."

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?)

HepCBC supports the following recommendations:

- Approval of tenofovir alafenamide (TAF) for use in adult patients with chronic hepatitis B, with acknowledgement that in some cases it could be the preferred, first line of treatment option; for example, in those now elderly or exhibiting signs of renal or bone disease, or not responding well to current treatment with ETV or TDF, or simply to prevent future renal or bone problems.
- Close monitoring of all patients on CHB treatment is required, whatever the regime. With TAF, we recommend particularly close monitoring of fasting LDL cholesterol, fasting glucose, and urine glucose.
- Close monitoring on both individual and population levels of possible development of resistance (not because there appears to be any increased danger of resistance, but simply because this development could have such serious consequences, particularly among the sex worker, MSM, and IVDU populations who are currently still spreading and contracting this disease). After all, this is the first new HBV treatment in a decade, so to quickly develop an alternative is unlikely.
- Doctors and specialists being mindful of contraindications and the importance of keeping abreast of emerging data reflecting "real world" use.
- While we applaud Gilead's announced generous inclusion of TAF into its patient support program, efforts by all stakeholders and agencies that have influence over pricing decisions should strive to ensure that all patients who would benefit from TAF have affordable access to it, regardless of lifestyle or insurance coverage.
- Further research into TAF's use among those co-infected with HIV, HCV, or both viruses, particularly among IVDU, sex workers, current and former prisoners, and men who have sex with men as they are more likely to be co-infected. This is a most critical research need.
- Further research in 'real world' usage into the place, if any, played by factors such as genotype, age, gender, lifestyle, presence of serological markers, etc. in response to TAF vs. other CHB treatments.
- Constant monitoring for drug interactions which may be unforeseen. The U. of Liverpool international drug reaction database should be consulted when prescribing any new medication to someone on TAF treatment.

References:

Evolving Options for HBV Therapy: Navigating the New Treatment Landscape (Clinical Care Options Power point presentation released October 10, 2017) https://www.clinicaloptions.com/Hepatitis/Treatment%20Updates/2017%20HBV%20Therapy/Downloadable%20Slideset/HBV_Treatment_Landscape_Slides.aspx [access on 2017-10-20]

Gilead Receives Approval in Canada for VEMLIDY™ (Tenofovir Alafenamide) for the Treatment of Chronic Hepatitis B Virus Infection (June 19, 2017) http://www.newswire.ca/news-releases/gilead-receives-approval-in-canada-for-vemlidy-tenofovir-alafenamide-for-the-treatment-of-chronic-hepatitis-b-virus-infection-629352103.html [accessed on 2017-10-20]

Management of chronic hepatitis B: Canadian Association for the Study of the Liver consensus guidelines (Cdn Assn for the Study of the Liver [CASL], Dec. 26, 2012) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3551569/ [accessed on 2017-10-20]

Primary Care Management of Hepatitis B – Quick Reference (HBV-QR) (Public Health Agency of Canada, Feb. 26, 2014) https://www.canada.ca/en/public-health/services/reports-publications/primary-care-management-hepatitis-b-quick-reference.html [accessed on 2017-10-20; problem at bottom of page 5 noted and passed along to Gilead]

Product Monograph Including Patient Medication Information PrVEMLIDY™ (May 17, 2017) http://www.gilead.ca/application/files/8514/9704/5557/vemlidy_pm_english.pdf [accessed on 2017-10-20]

Report on Hepatitis B and C in Canada: 2014 (Public Health Agency of Canada, published 2017) https://www.canada.ca/en/services/health/publications/diseases-conditions/report-hepatitis-b-c-canada-2014.html [accessed on 2017-10-20]

Prices of Hepatitis B drugs from BC Pharmacare info sheet referencing CADTH/CDR report: https://www2.gov.bc.ca/assets/gov/health/health-drug-coverage/pharmacare/tenofovir-alafenamide-3557-info.pdf [accessed Feb. 21, 2018]

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.