Common Drug Review
Patient Group Input Submissions

Request for Advice: ombitasvir/paritaprevir/ritonavir and dasabuvir (Holkira Pak) for chronic hepatitis C

Patient group input submissions were received from the following patient groups. Those with permission to post are included in this document.
Action Hepatitis Canada — permission granted to post
Canadian Liver Foundation — permission granted to post
Canadian Treatment Action Council — permission granted to post
HepCBC Hepatitis C Education and Prevention Society — permission granted to post
Pacific Hepatitis C Network — permission granted to post

CADTH received a request for advice from the drug plans participating in CADTH Common Drug Review. Advice was sought regarding alignment of the CDEC recommendations for CADTH's therapeutic review on drugs for hepatitis C and for the four earlier CDEC recommendations for Harvoni, Holkira Pak, Sovaldi and Daklinza.

We asked patient groups is there anything the CADTH review team and expert committee (CDEC) should be aware or reminded of, if updating individual recommendations for Harvoni, Holkira Pak, Solvaldi and/or Daklinza?

CADTH received patient group input for this review on or before February 25, 2016.

The views expressed in each submission are those of the submitting organization or individual; not necessarily the views of CADTH or of other organizations. While CADTH formats the patient input submissions for posting, it does not edit the content of the submissions.

CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no personal information is included in the submission. The name of the submitting patient group and all conflict of interest information are included in the posted patient group submission; however, the name of the author, including the name of an individual patient or caregiver submitting the patient input, are not posted.

Action Hepatitis Canada

We were pleased to see that the Canadian Agency for Drugs and Technologies in Health (CADTH)'s *Therapeutic Review: Drugs for Chronic Hepatitis C Infection: Recommendations Report* issued as its primary recommendation that all patients with Chronic Hepatitis C (CHC) infection be considered for treatment. This recommendation is supported by clinical evidence and acknowledges the desire of Canadians to access the most effective, least toxic treatments on the market to address their health conditions.

The *Recommendations Report* outlines the benefits of DAA treatment for all patients living with CHC, recognizing that the excessive prices of these medicines may cause payers to ration their access. In cases where payers determine a need to limit access to treatment, CADTH recommends that treatment priority be given to patients with more severe disease.

The unreasonably high prices of new CHC treatments are a result of pharmaceutical industry taking advantage of international and domestic medicine pricing policies which prioritize corporate profit over the health and well-being of people. Pharmaceutical companies will continue to over-charge, seeking the highest prices possible for their medicines, until Canadian and international governments address the system that allows for such greed. Addressing faulty pricing policies is not the mandate of CADTH, nor is it within CADTH's mandate to determine what payers can and cannot pay for treatments.

Canadian Drug Expert Committee (CDEC) recommendations for Harvoni, Sovaldi, Holkira Pak and Daklinza should be updated to align with the recommendations from the Therapeutic Review. Clinical criterion in all cases should be updated to encompass all Canadians living with CHC. Sections entitled 'Conditions" should clearly indicate that inflated pricing may be a factor that limits access for each of these medicines.

CDEC recommendations should acknowledge that while these new drugs are cost-effective at high prices, the same high prices may cause payers to have difficulty covering all patients who would benefit from treatment. Payers should seek price reductions. In cases where the prices remain too high limiting access, priority for treatment should be given to patients with more severe disease.

We appreciate the recommendations in the Therapeutic Review of Drugs for Hepatitis C as we believe they align with evidence as well as with the needs and rights of Canadians. It is our hope that these recommendations will support payers to follow the lead of some of our provinces including New Brunswick, Prince Edward Island and Quebec who have established plans that balance access and cost, ensuring treatment for people living with CHC. It is also our hope that our federal government will see the example of hepatitis C medicines as motivation to review and update regulatory frameworks involved in the establishment of pharmaceutical pricing in Canada.

Canadian Liver Foundation

Thank you for offering the Canadian Liver Foundation (CLF) the opportunity to provide advice regarding the ways in which the CDEC recommendations for Sovaldi, Harvoni, Holkira Pak and Daklinza can be revised in order to better inform the provincial drug plans.
CADTH's recent report on its Therapeutic Review of Direct-Acting Antivirals for Hepatitis C was a thorough and evidence-based document. The report accurately captures the prescribing parameters and costs of drugs used to treat hepatitis C. The models CADTH employed in its analysis reflect the true nature of the disease as we currently understand it. However, there are some aspects that require additional comment, especially as the idea is to update the previously published CDEC recommendations to align with the report.

Treatment criteria:

- There is an inconsistency between the report and the recommendations for Holkira Pak, Harvoni and Sovaldi. The report indicates that all patients would be treated, but the recommendations for these agents specify that treatment should only be reimbursed for those with stage 2 or higher fibrosis. The individual CDEC recommendations for these therapies should not include fibrosis level criteria for treatment in order to align with the report.
- HCV is the only curable infection for which funding of therapy is restricted only to advanced disease.

Genotypes 4, 5, 6:

- There are no recommendations about treatment of genotypes other than 1, 2 and 3. There is data that has been presented publicly, although not published in manuscript form, that indicates that patients with genotypes 4, 5 and 6 respond just as well to sofosbuvir-based regimens. Currently there is no all-oral treatment for these patients who are mostly immigrants from South East Asia and Africa. Refusal to provide all-oral treatment for these patients amounts to discrimination. They cannot advocate for themselves. While they can still be treated with interferon-based therapy, the low response rates do not make this a satisfactory option especially when treatment comes with debilitating interferon-based side-effects.
- Response rates for genotypes 4, 5 and 6 with all-oral therapy are better than 90%. Given that infection with genotypes 5 and 6 is uncommon in North America and Europe, it is unlikely that there will be large scale studies in the near future to use as reference for reimbursement recommendations. Harvoni is approved for genotype 4 in the USA and Europe and Technivie is approved for genotype 4 in most markets including Canada. Harvoni is also approved for genotypes 5 and 6 in the USA. The CDEC recommendations should follow the recommendations of the Canadian Association for the Study of the Liver (CASL) Consensus Guidelines that recommend 12 week regimens of Harvoni or Technivie for genotype 4, Sovaldi (plus PEG/RBV) for genotype 5 and Harvoni for genotypes 6.
- Zepatier, the latest entrant to the hepatitis C drug therapy market, is also licensed for treatment of genotype 4. CADTH must make a positive statement about treatment of genotypes 4-6. It makes no sense to exclude published data, even if not peer-reviewed, because it would mean that the CADTH document would be out of date as it is published.

Pan-genotypic therapy:

- In the coming year, the combination of sofosbuvir and velpatasvir will be licensed for all genotypes. Therefore, it makes sense to include this combination in the next edition of the report.

Mixed genotypes:

- We have come across a problem in some provinces in that they are not reimbursing treatment for mixed genotypes. While it is uncommon for a patient to be infected with more than one genotype of the hepatitis C virus, without reimbursement there are no treatment options. CADTH should address this issue by noting that the rarity of this occurrence means there will never be a clinical trial in this population. It should further be noted that as long as the antivirals that are prescribed adequately cover both genotypes, the response rates are likely to be no different than for mono-infected. For example, currently a mixed genotype1- genotype 2 infection should be treated with Harvoni and ribavirin for 12 weeks. Unless CADTH makes a statement about these patients, they are unlikely to ever be treated.

Extra-hepatic disease:

- CADTH has never made any recommendation to fund treatment for a patient with significant extra-hepatic disease even if the patient is F0-1, as highlighted in many treatment guidelines. Some provinces fund these through an "exceptional status" mechanism, but others do not. There are very few of these patients, so the financial implications are tiny, but the clinical impact is significant.

Assessment of fibrosis:

- Most provinces have followed the previous CADTH recommendations and restricted treatment to those with stage 2 disease or higher. Setting limits like this leads to a sense of precision that does not exist. First, liver biopsy, on which the METAVIR scoring system is based, under-calls the true stage of fibrosis in ~30% of cases. Second, the various measures of fibrosis, including Fibroscan, Fibrotest, the ELF score and the APRI score do not correlate 100% with the biopsy appearances, nor with each other. F2 on Fibroscan might be F1 on Fibrotest, and vice versa. Thus to set a hard limit such as F2 means that a significant number of patients who genuinely have stage 2 fibrosis will not get treatment (and conversely, some who the provinces do not want to fund will get treatment). This is essentially unfair, and argues for removal of fibrosis restrictions.

Hepatitis C treatment is a rapidly evolving field with new agents entering the market each year. We appreciate that CADTH must follow its established review procedures, but it is important that reimbursement recommendations keep pace with the available research in order to make the most effective therapies available to all patients regardless of their genotype. It is our hope that this retrospective review of existing CDEC recommendations in light of new research will prompt the provinces to make more inclusive reimbursement decisions. In order to one day eliminate hepatitis C, we need to treat as many patients as possible and this will only be possible with less restrictive criteria.

Canadian Treatment Action Council

CANADIAN TREATMENT ACTION COUNCIL

CTAC is Canada's non-governmental organization led by and for people living with HIV and HIV/Hepatitis C co-infection, focusing on access to treatment. Since 1996, we have been working to secure and ensure equitable, affordable and timely access to treatment, care, and support for people in Canada living with HIV and HIV/Hepatitis C co-infection. We work with community, public, private and not-for-profit leaders to inform research and public policy, and promote public awareness and discussion. CTAC enjoys membership in the national coalitions *Action Hepatitis Canada* and *Best Medicines Coalition*.

CTAC welcomes the opportunity to engage in the regulatory process at every opportunity and has been pleased to be recognized by CADTH several times for excellence in our prolific submission of patient input. In this spirit of cooperation and collaboration, we are excited to offer the following responses, suggestions, and endorsements of CADTH's November 2015 *Therapeutic Review of Drugs for Chronic Hepatitis C Infection* (hereafter referred to as *Therapeutic Review).*

HEPATITIS C IN CANADA TODAY

According to 2011 data provided by the *Public Health Agency of Canada* (PHAC), there are at least 250,000 Canadians living with Hepatitis C (HCV), and Canada is incurring thousands of new infections each year.[1] However, Canada has a distinct data problem in estimating its national burden. 2011 data from PHAC does not statistically differentiate between acute resolved infection, clearance, and chronic infection.[2] Based on this discrepancy, many in the public health sector consider this burden estimate to be much lower than the actual. Furthermore, modeled estimates of prevalence and burden have suggested that approximately half of all Canadians living with HCV are unaware of their status.[3] Lack of awareness of status is particularly problematic, as HCV can be largely asymptomatic for many years; a patient may feel well-enough while consistently incurring liver damage, contributing to greater health issues over several years. As a result, HCV is the leading cause of liver cancer and liver transplant in Canada.[4] Furthermore, the impact of HCV on a patient's daily life is significant, with several patients consulted by CTAC reporting "fatigue, insomnia, constant (daily) headaches, weight-loss, suppressed appetite, hair-loss, some cognitive difficulties such as word recall, depression, irritability, quickness to anger, short term memory loss, and joint pain."[5]

Earlier interventions, in the form of diagnostic screening and education, could help alleviate these rising numbers and help avoid the 30-50% of all liver cancers that the *Canadian Liver Foundation* argues can be attributed to HCV.[6] Consider then, that liver cancer is the primary cause of death of patients living with HCV worldwide,[7] and that it is also the only cancer in Canada whose rates and mortality are

[1] Trubnikov M, et al. *Estimated Prevalence of Hepatitis C Virus Infection in Canada, 2011* .Canada Communicable Disease Report CCDR. Vol. 40, No. 19, December 2014.
[2] *Liver Disease in Canada: A Crisis in the Making*. Canadian Liver Foundation, March 2013.
[3] Trubnikov M, et al. *Estimated Prevalence of Hepatitis C Virus Infection in Canada, 2011*. *Canada Communicable Disease Report*: Volume 40, No. 19, December 2014.
[4] Myers RP, et al. *Burden of Disease and Cost of Chronic Hepatitis C Virus Infection in Canada*. Canadian Journal Gastroenterology and Hepatology. Vol. 28, No. 5. May 2014.
[5] CTAC Patient Input Submissions: Holkira Pak, Harvoni, Sofosbuvir.
[6] *Hepatitis C Education Day: Toward Elimination of Hepatitis C in Ontario.* Canadian Liver Foundation. Presentation delivered at Queen's Park Ontario Legislature, November 25th, 2014.
[7] De Oliveria Andrade LJ, et al. *Association Between Hepatitis C and Hepatocellular Carcinoma*. Journal of Global Infectious Diseases. Vol. 1, No. 1. January 2009.

increasing,[8] and we are forced to evaluate the economic gains to be had in recognizing HCV treatment as an integral part of cancer prevention. In fact, there is much consensus among hepatologists and oncology researchers that the increased prevalence of advanced liver disease in Canada can be attributed to increased exposure to hepatitis C.[9]

Despite the wide-reaching impact of HCV on Canadians, Canada is woefully behind in addressing the epidemic. While HCV death rates exceed HIV, Canada has spent only one-tenth on HCV research as it has on research on HIV.[10] Even in the face of the most robust development pipeline of HCV meds in history, Canada lacks the political will to sincerely address access to life-saving cures, and has failed to recognize how that increased access will benefit Canadians living with HCV. Likewise, Canada has failed to acknowledge HCV treatment as an important part of preventing advanced liver disease and cancer. Canada lacks federal screening guidelines from PHAC and has not developed a national strategy to address the epidemic, leading to low rates of screening and diagnosis. In fact, at the present rates of screening, treatment, and diagnosis, new HCV infections will increase, as will corresponding health care costs in the form of liver transplants, treatment of liver cancer, and other liver diseases.[11]
The HCV epidemic in Canada is an impending health care crisis but CTAC is encouraged by CDEC's recommendation that all HCV patients be treated regardless of fibrosis score.

COST CONTAINMENT AND HEALTH SYSTEM SUSTAINABILITY AT F0

CTAC endorses all 4 of CDEC's treatment recommendations as presented in the *Therapeutic Review.* Of particular importance is Recommendation One, which recommends that "all patients with CHC infection should be considered for treatment, regardless of fibrosis score."[12] Recommendation One has also accounted for cost-effectiveness and "health system sustainability," arguing in favour for priority treatment of patients with greater need.[13] CTAC interprets this as a continued advisory to CADTH jurisdictions that, while treating F0 is optimal, patients with more fibrosis should be prioritized.
Clinical evidence is unanimous in its conclusion that earlier treatment of HCV is associated with better health outcomes, and CTAC celebrates the CDEC recommendations as being in line with the global trend toward treating HCV as early as possible. In fact, CTAC chooses to read CDEC's recommendations as an important step toward provoking a National Strategy on HCV in Canada, which would allow Canada to comply with the 2014 World Health Organization's resolution requesting members to "develop and implement coordinated multisectoral national strategies for preventing, diagnosing, and treating viral hepatitis."[14] Canada has no such plan, but in a distinct representation of how Canada *does* federalism conceptually, we have all the separate pieces of that infrastructure, without a central guidance or strategic vision to unite them.

[8] Naghavi, M., et al. *Global, Regional, and National Age-Sex Specific All-Cause and Cause-Specific Mortality for 240 Causes of Death, 1990-2013: A Systematic Analysis for the Global Burden of Disease Study 2013*. Lancet. Vol. 385, No. 9963. January 2015
[9] Myers, RP, et al. *Burden of Disease and Cost of Chronic Hepatitis C Virus Infection in Canada*. Canadian Journal Gastroenterology and Hepatology. Vol. 25, No. 5, May 2014.
[10] *Liver Disease in Canada: A Crisis in the Making*. Canadian Liver Foundation, March 2013.
[11] Trubnikov, M, et al. *Identifying and Describing a Cohort Effect in the National Database of Reported Cases of Hepatitis C Virus Infection in Canada (1991-2010): An Age-Period-Cohort Analysis.* Canadian Medical Association Journal. OPEN. Vol. 2, No. 4. October-December 2014.
[12] *Drugs for Chronic Hepatitis C Infection: Recommendations Report*. Ottawa: CADTH Therapeutic Review; Vol.3, No. 1. November 2015
[13] *Drugs for Chronic Hepatitis C Infection: Recommendations Report*. Ottawa: CADTH Therapeutic Review; Vol.3, No. 1. November 2015.
[14] Hepatitis. World Health Assembly Resolution 67.6. May 2014.

CTAC implores that CADTH advise jurisdictional participants of the existence of new, public-health minded approaches to HCV in Canada. Here we suggest a thorough review of the model adopted by the National Institute for Excellence in Health and Social Services (INESSS) in Quebec, which scales back fibrosis criteria for access to Harvoni and Holkira Pak over a period of 6 years.[15] In year 1, only patients with fibrosis scores of F3 and F4 will be treated, but by years 4, 5, and 6, INESSS recommends that eligibility criteria fall to F0, treating all patients diagnosed with chronic HCV.[16] Even the traditionally restrictive and access-conservative Corrections Services Canada formulary has stated that they "agree in principle" with CDR recommendations of new DAAs, and have committed to identifying "training needs, updates needed to the Hep C protocols."[17]

While the Quebec model is expected to cost up to $546 million over the final 3 years of its scale-back (treating those with zero fibrosis at that point), they still constitute savings when compared to the cost of non-treatment.[18] Nowhere was this better summarized than by Brett Skinner, executive director of Rx&D Canada, when he argued that "the cost of these drugs is really a bargain compared to the alternative, which is either no treatment, poor treatment or much more expensive treatment options."[19] However, we need not rely solely on Mr. Skinner's astute testimony, rather the cost-data also speaks to Health Care savings incurred through coordinated, strategic spending on medications. In 2013, a report commissioned by the *Conference Board of Canada* concluded that "the $1.22 billion spent on pharmaceutical treatments in 2012 generated offsetting health and societal benefits of nearly $2.44 billion."[20] Moreover, savings are also evident at the level of individual patients. The price of treatment in Canada can be approximately $55,000-$70,000 per cure, however, in the absence of that cure, we can estimate the costs of a patient incurring cirrhosis, developing liver disease (possibly liver cancer), and liver transplant to be upwards of $320,000 per patient.[21]

Cost still serves to discourage many patients from seeking treatment, adding another destructive element to the cost environment in Canada. CTAC patient input surveys routinely ask patients to explain barriers to initiating treatment. By far, the most common response was that "cost is the biggest one."[22] Patients are also particularly cynical when explaining eligibility criteria as a barrier, and specifically a very counterintuitive barrier: most Canadians do not expect their much-celebrated Health Care system to deny a cure to patients who are *not sick enough*. As one patient stated, in addressing barriers and stigma, a significant problem for patients is "not being taken seriously until their health is seriously compromised. Also not being able to get funding for certain treatments"[23] in specific jurisdictions. There is no question that HCV cures are exceedingly expensive and contribute to the complexity of addressing the epidemic. However, Canada enjoys several institutional mechanisms to review and negotiate the costs of pharmaceutical medications, in the pan-Canadian Pharmaceutical Alliance (pCPA) as well as the Patented Medicines Review Board (PMRB). Despite this infrastructure allowing for negotiation, Canada pays some of the highest drug prices in the world.[24] In the realm of HCV, this is not

[15] *Harvoni et Holkira Pak – Hepatite C Chronique de Genotype 1*. Quebec: INESSS; 2015 Jui. (INESSS Recommendations).
[16] *Harvoni et Holkira Pak – Hepatite C Chronique de Genotype 1*. Quebec: INESSS; 2015 Jui. (INESSS Recommendations).
[17] Correctional Services Canada. *National Pharmacy & Therapeutics Committee Meeting Record of Decisions, October 2015.* Obtained through ATIP (Access To Information and Privacy) Request to Correctional Services Canada. Pg 2.
[18] Seidman, Karen. *The Cost of Emerging Drugs: Quebec's Wrenching Choices.* Montreal Gazette. Aug 22nd, 2015.
[19] Seidman, Karen. *The Cost of Emerging Drugs: Quebec's Wrenching Choices.* Montreal Gazette. Aug 22nd, 2015.
[20] Hermus, Greg. Et al. *Reducing Health Care and Societal Costs of Disease: The Role of Pharmaceuticals.* Conference Board of Canada. July 2013.
[21] *Liver Disease in Canada: A Crisis in the Making*. Canadian Liver Foundation, March 2013.
[22] CTAC Patient Input Submissions: Sovaldi, Harvoni.
[23] CTAC Patient Input Submission: Holkira Pak, Sovaldi, Harvoni, Daklinza.
[24] Gagnon, Marc-André. *A Roadmap to Rational Pharma-Care Policy in Canada*. Canadian Federation of Nurses Unions. 2014.

because the medicines themselves are costly to make, but rather that the epidemic has made their value to Canadians high.[25] However, the robust and dynamic HCV pipeline should also contribute to further health system savings. As more manufacturers enter the HCV treatment market, many researchers hope for a leveling of pricing to respond to increased market competition. Patients with whom CTAC has consulted have reiterated this anticipation, with one patient remarking "were I to obtain SVR...my quality of life would improve immeasurably, physically and mentally. And potential long-term costs to the health care system would, of course, be reduced...and likely lower the cost of medication."[26]

Beyond the costs to be saved in responding to the epidemic, there are tremendous *human* savings to be had. If we consider that the return on investment of a coherent Health Care system is the production and maintenance of healthy citizens, we must take seriously the impact of successful treatment. Many patients were enthusiastic to share with CTAC how their life was drastically improved by successful treatment. Thanks to a cure, one patient noted that their quality of life was absolutely improved; "now, after over 4 years since finishing treatment, I have much more energy, no cognitive/speech difficulties, and fewer psychological instances."[27]

Regardless of one's preferred argument, there is money to be saved in curing hepatitis C: in curing those patients living with HCV and returning them to work; in preventing the most impactful and lethal cancer in Canada; and in demonstrating to Canadians that our health care system can face – and beat - a curable epidemic.

THE CONTINUED ROLE OF RIBAVIRIN

In April of 2015, CTAC was consulted by CADTH Impact and Evaluations Officer, Andrew Dzuba, to participate in Informant Interviews regarding reform of the *Common Drug Review* (CDR). Only 5 of the 114 most prolific submitters of patient input were involved. In June of 2015, CTAC was recognized as being in the top 15% of agencies regularly providing patient input to CADTH. CTAC is excited to consistently participate in the patient input process and is pleased to be recognized for excellence in this capacity. In developing this expertise, CTAC has provided many patient input consultations on HCV treatments, receiving plentiful data from Canadian patients and caregivers on their experience of HCV and its cures. It is from this perspective that CTAC shares patient feedback received regarding the continued inclusion of *Ribavirin* (RBV) as a component of some HCV regimens for certain patients. CTAC was requested by CADTH to elaborate on our patient submissions' remarks on RBV.

CTAC acknowledges the evidence suggesting clinical benefit associated with RBV in some patients. Specifically, that certain genotypes, certain past-treatment experiences, and certain states of liver health, appear to benefit from the continued inclusion of RBV. RBV continues to be recommended by CADTH for use in treatments for: genotype 1A patients using Holkira Pak; genotype 2 patients; genotype 3 cirrhotic patients; and genotype 4, treatment-naive, non-cirrhotic patients.[28]

CTAC has received consistent feedback from patients that adverse events and side effects associated with RBV merit further consideration against their therapeutic benefit. Many comments from patients echo clinical findings suggesting a relationship between RBV and dermatological events, pruritus, and

[25] *Costly Cures*. The Economist. June 2014.
[26] CTAC Patient Input Submission: Holkira Pak.
[27] CTAC Patient Input Submission: Holkira Pak.
[28] *Drugs for Chronic Hepatitis C Infection: Recommendations Report*. Ottawa: CADTH Therapeutic Review; Vol.3, No. 1. November 2015.

skin rashes sometimes necessitating hospital attention.[29] Holkira Pak trials *PEARL, TURQUOISE, and SAPPHIRE,* provided data suggesting that as many as 90% of all 2700 patients in those studies suffered at least one adverse event, with the most dire incidences being attributed to *Ribavirin.*[30] While the impact of RBV is not as intolerable as *Pegylated Interferon*, a previous standard of care, patients routinely cited it as an artifact of a past treatment era. Indeed, though many patients celebrated the "end of the interferon era," as many more were concerned that RBV remained in some regimens. Some patients referred to RBV as "poison"[31] and more expressed reticence to endorse a regimen containing RBV, with one patient arguing they'd avoid such treatments, fearing that "side effects would do me in."[32] In response to a survey question asking why a patient might or might not take a particular treatment, several patients cited RBV-related side-effects, with one patient responding "No. More ribavirin, that's why."[33]

In reviewing the evidence base, CTAC concurs that RBV maintains a role in HCV treatment, and specifically so in the criteria proposed by the *Therapeutic Review*. However, we urge CDEC to consider the impact of RBV on the patient when considering its inclusion in their treatment recommendations. Further, CTAC has shared this observation to manufacturers, choosing to frame RBV as the *next* medication to eliminate from HCV treatment, having already successfully done so with *Pegylated Interferon* for most patients.

SUMMARY OF RECOMMENDATIONS

CTAC endorses all 4 recommendations made by CDEC in the *Therapeutic Review*. We celebrate CDEC's F0 recommendation as an important step in improving access to a cure for thousands of Canadians, and an integral part of developing a National Strategy to address the epidemic. We hope that CADTH will respond to our call and act as advisor and mediator to its jurisdictional members, actively alerting public payer programs to the existence of models from which to draw inspiration and influence. Specifically, CTAC endorses an approach similar to the INESSS model of scaling back fibrosis criteria over time, while still prioritizing our hardest-to-treat patients first. We have argued that this model, and similar ones, satisfy health system sustainability and even improve health care returns and expenditures. We do not argue that jurisdictional programs adopt this model wholesale, but rather encourage them to remodel and repurpose a scaling-back model with their own budgets, priorities, and needs in mind. Further, CTAC reminds CDEC and CADTH that the return on investment from Health Care spending is not solely to be estimated in dollars and cents of budgetary savings, but rather the reduced health care spending in improved health outcomes resulting from treatment, and the improved quality of life of thousands of Canadians returning to work and their daily lives.

[29] CTAC Patient Input Submission: Holkira Pak.
[30] CTAC Patient Input Submission: Holkira Pak.
[31] CTAC Patient Input Submission: Holkira Pak.
[32] CTAC Patient Input Submissions: Holkira Pak, Harvoni.
[33] CTAC Patient Input Submission: Holkira Pak.

Finally, the narrative and trajectory of hepatitis C through our regulatory systems highlights several inequities, from Health Canada to the CDR to the provincial formularies. That Health Canada's *Therapeutic Products Directorate* and the CDR duplicate some functions; that the CDEC recommendations are not binding; that the provinces and territories then conduct similarly duplicative reviews; all contribute to an incoherent and inefficient response to an epidemic that is poised to severely impact Canada's ability to best serve its citizens. We sincerely hope for the broad acceptance of these recommendations by the provinces and territories, and where programs are unable to implement F0 criteria for access, that these programs seriously consider the development of a phased approach, similar (but not identical) to INESSS. Such uncharacteristic consensus and application by the provinces would build the foundation for a very effective, if nascent, National Strategy to end the HCV epidemic in Canada.

HepCBC Hepatitis C Education and Prevention Society

General Recommendations:
(a) HepCBC supports the CDEC recommendations that all patients with CHC should be considered for treatment, regardless of fibrosis score. We recognise priority needs to be given to those with advanced liver disease, according to the concept of Treatment as Prevention of morbidity/mortality. However there is also clear evidence that the sooner hepatitis C treatment is given, the greater the chance of achieving SVR, the greater chance that liver cancer (and cancer in general), liver failure and transplant, plus other morbidities and mortality will be prevented, and the greater number of QALYs gained.
(b) HepCBC also supports the addition of one-time-only age-cohort testing for hepatitis C to the current Canadian hepatitis screening guidelines. This action could result in identifying and being able to treat almost every Canadian with hepatitis C. This would greatly enhance the total benefit of these medications to our society as well as providing a good rationale for the TCPA to negotiate lower prices per treatment.

Recommendation for: Holkira Pak™ (treatment for CHC, genotype 1):
HepCBC supports the CDEC recommendation for Holkira Pak™ as an approved treatment for CHC genotype 1 patients with modifications as follows:
1. Genotype 1a:
– paritaprevir/ritonavir/ombitasvir + dasabuvir + ribavirin for 12 weeks (without cirrhosis)
– paritaprevir/ritonavir/ombitasvir + dasabuvir + ribavirin for 12-24 weeks (with cirrhosis)

2. Genotype 1b:
– paritaprevir/ritonavir/ombitasvir + dasabuvir for 12 weeks (without cirrhosis)
– paritaprevir/ritonavir/ombitasvir + dasabuvir + ribavirin for 12 weeks (with cirrhosis)

The recommendations for Holkira Pak™ are supported by:
EASL guidelines:
http://www.easl.eu/medias/cpg/HEPC-2015/Full-report.pdf

AASLD guidelines:
http://www.hcvguidelines.org/

CASL guidelines:
http://www.liver.ca/files/Professional_Education___Partnerships/Information___Resources_for_HCP/CASL_Hep_C_Consensus_Guidelines_Update_-_Jan_2015.pdf

Patient Attitudes towards Ribavirin Changing: A report from a hepatitis C patient group as requested by CADTH submitted by HepCBC Hepatitis C Education and Prevention Society February 15, 2016

SUMMARY: We looked at how ribavirin is used in current hepatitis C treatments, and some current presentations about ribavirin aimed at the medical profession, then decided to do our own very informal poll of patients recruited through an article in our online monthly newsletter. We got some very interesting results which we include below. Our conclusions:

(1) Almost half of patients (47.4%) said they take whatever their doctor recommends. Only 10.5% said they would never take ribavirin. The remainder compared the benefits versus the drawbacks and felt the use of ribavirin is justified in contexts where it gives them an increased chance of a sustained viral response (SVR). The average minimum increased chance of gaining SVR which they would accept was 18% (range 1 – 30%). Clearly, the higher the benefit (difference in % of SVR attained with ribavirin vs. without it), the more patients are willing to take ribavirin. However, there are a few patients who will simply refuse to take anything with ribavirin in it.

(2) The patients who had taken both interferon-containing medications (unsuccessfully) and later, a new DAA +ribavirin for 12 weeks all said the side-effects were either non-existent or far less serious in the later treatment, and all happily achieved SVR (except one who is undetectable but still awaiting SVR verification).

(3) We also saw a need for physicians and/or nurses to counsel patients being prescribed one of the new DAA treatments including ribavirin who may be reluctant to take it:

• Compared to other ribavirin treatments patients may have heard about, current ribavirin treatments do not generally contain interferon, boceprevir, or telaprevir. These three ingredients may have been responsible for side-effects patients have heard about. Because of this, the side-effects of another drug may have been incorrectly ascribed to ribavirin.
• The side-effects of ribavirin are cumulative, developing and worsening over time. Current ribavirin-containing treatments are typically 8-16 weeks, so in many cases side-effects may not even have time to show up before the treatment is over.

FACTS we worked with:
• GT1a cannot take Holkira Pak without ribavirin.
• GT1b cirrhotics cannot take Holkira Pak without ribavirin.
• GT2 have little option but to include ribavirin, especially if they fail sofosbuvir+daclatasvir.
• GT3 often need ribavirin.
• SVR rates have been shown to be improved in other GT cirrhotics if ribavirin is included.
• Ribavirin generally has “a bad name” among patients.

SOURCES: We saw confirmation in Professor Graham Foster’s video (https://www.youtube.com/watch?v=vCcpES8O6P0 from the Viral Hepatitis Congress in Germany on 10-12 Sept., 2015) that ribavirin still is included for some genotypes, stages of liver disease, and other conditions, and why.

We also saw an interesting discussion of HCV resistance and ribavirin at http://www.clinicaloptions.com/Hepatitis/Treatment%20Updates/HCV%20Resistance%20Alert/Clinical%20Thoughts/CT2.aspx

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OUR ONLINE (Doodle) POLL (ran online Feb. 3-15, 2016)
Recruiting and characteristics of participants = readers of February issue of bulletin Hep C Bull (http://hepcbc.ca/wp-content/uploads/minutes-agendas-newsletters/hepc-bull_2016-02-01.pdf)

Number of participants = 19

TEXT: Ribavirin's side-effects can be awful. However it is cheap, has no long-term effects, and when combined with new HCV treatments, can boost the chance of a cure for some genotypes, or for those with cirrhosis. It also can prevent drug-resistance when re-treating. OUR QUESTION: How many percentage (%) points IMPROVEMENT IN YOUR CHANCE OF A CURE would be necessary for YOU to take (or re-take) a new HCV treatment with added ribavirin for 12-16 weeks? Select the answer closest to your own feelings about this

ANSWERS to each of the Choices:
At least 1% improvement necessary = 1/19 = 5.3%
At least 5% improvement necessary = 1/19 = 5.3%
At least 10% improvement necessary = 1/19 = 5.3%
At least 20% improvement necessary = 1/19 = 5.3%
At least 30% improvement necessary = 3/19 = 15.8%
I will never take ribavirin = 2/19 = 10.5%
I take anything my doctor recommends = 9/19 = 47.4%
Did not select any answer; left comment instead = 1/19 = 5.3%

PATIENT COMMENTS:
Comment #1:
I was treated and cured with a triple combination which included Ribavirin after relapsing after my first treatment with Interferon and Ribavirin only. The side effects were awful including rosacea, however all the skin side effects were gone soon after my treatment was finished. It was gruelling going through the treatment, however it was very much worth the result - I'm cured! [NOTE: This patient's side-effects could have been due to interferon and the 1st generation DAA, as well as ribavirin; hard to 'tease out' in this case]

Comment #2:
Took Ribavirin 3 different times. First 2 times I had to give up or would have killed me. The last time I was on a drug study for sofosbuvir and ribavirin. For 12 weeks, it made me sick but cleared my hep-c on the third week.

Comment #3:
My choice was made to go ahead with peg interferon /ribaviron only because I trusted my doctor's judgement in this case. Otherwise I may not have.

Comment #4 (from patient who got HCV from blood transfusion 1955, genotype 2):
The poll wasn't really relevant to my situation since I hadn't even considered side effects of Ribavirin. I just knew I couldn't tolerate Interferon, so waited 20 years until something came along that didn't include it and offered potentially good results. SOF with RBV was nothing like Interferon!!!! [This patient sent the chart below comparing side-effects experienced during the 2 treatments, stand-alone interferon for 5 months versus sofosbuvir+ribavirin for 12 weeks:]

1995 IFN (Intron A), 3 injections /week, dosage reduced twice and discontinued by doctor at 5 months - unsuccessful
- extreme fatigue
- insomnia
- nausea, vomiting
- early hallucinations
- joint and muscle pain
- headaches
- hair loss
- severe itching
- depression
- weight loss/ loss of appetite
- chills /shivering, mild fever
- persistent cough,
- sore throat
- back ache
- pain around liver
- nose bleeds, bleeding gums, mouth sores
- diarrhea

2015 SOF with RBV-12 weeks: SVR not confirmed yet but HCV undetectable at end of treatment
- fatigue
- insomnia
- early mild nausea, dizziness
- lower abdominal pain
- irritability/ impatience
- constipation

Comment #5 (Patient with genotype 1b):
(1) Treatment with interferon plus ribavirin for 48 weeks. Completed treatment though side-effects terribly debilitating. Partial response only.
(2) Another treatment with interferon (unknown whether stand-alone or not) for 30 weeks. Had to be pulled off due to side-effects.
(3) Now cirrhotic, in early 2015 he took 12 weeks of Holkira Pak™ with ribavirin. He has been virus-free for 9 months (Feb., 2016). He experienced NO side-effects with this treatment.

Pacific Hepatitis C Network

Submission type	Requests for Advice Regarding CDEC Recommendations for Hepatitis C Drugs
Name of the patient group	Pacific Hepatitis C Network
Name of the primary contact for this submission:	[redacted]
Position or title with patient group	[redacted]
Email	[redacted]
Telephone number(s)	[redacted]
Name of author (if different)	
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Permission is granted to post this submission	Yes

Impact of Condition on Patients
Our members have described hep C as a disease that kills slowly by degrees, a disease that is able to affect all aspects of life piece by piece before it takes it.

Hepatitis C (HCV) is a serious and potentially life-threatening liver disease. It may lead to liver cirrhosis, cancer, liver failure, and even death. However, in many cases those life-threatening HCV developments only occur after patients spend time, sometimes years, worrying, rearranging their lives around HCV symptoms, and dealing with the psychological toll of having a communicable disease that many people fear and have misconceptions about.

Hepatitis C symptoms are numerous and affect patients differently. Symptoms, reported by our members, range from “have not had hep C symptoms” to “having muscle and joint pain” to affecting one’s daily life.

“Brain fog”, for example, is a common symptom of hep C that affects one’s daily life. The experience of “brain fog” includes difficulty thinking, remembering, understanding, and focusing. It can be very disabling, impacting negatively on a person’s ability to function at home and in the workplace.

People with “brain fog” describe having to take manual jobs requiring less cognitive function, even though this can pose other challenges if that work requires physical labour of any kind as fatigue is sometimes also a symptom of hepatitis C.

In addition, comments received about how HCV impacts quality of life were: “It all depends on the amount of fatigue I feel, if bad it is a stay at home day and I was at one time a active person”, as well as,

"work--I am too tired for the physical demands of my work", and "I am extremely exhausted most of the time."

Furthermore, hep C doesn't only take a physical toll on patients, but takes psychological and emotional tolls on patients and their support networks as well. This is due, in part, to the fact that it is a disease that one often has to wait and get sicker before receiving treatment, but, at the same time, is a disease that patients may get irreversibly sicker or die of before they find a treatment able to treat their hep C.

Hepatitis C also makes one's health unreliable, leaving patients wondering if they would have taken more chances, in their social life and their career, if they weren't always concerned that their health wasn't up to the challenge.

Lastly, these physical and psychological tolls are often worsened by a social isolation, which often comes from suffering fatigue, other hep C symptoms, the worry of passing HCV on, and/or from the stigma that comes as a result of having hepatitis C, a communicable disease.

Requested Advice Regarding CDEC Recommendations for the 4 Hepatitis C Drugs

Pacific Hepatitis C Network (PHCN) believes that a framework that allows the widest possible target patient group access to care and support would be ideal. PHCN believes that the CDEC recommendations for Harvoni, Sovaldi, Holkira Pak, and Daklinza should be updated to align with the CDEC recommendations outlined in the *Therapeutic Review of Drugs for Chronic Hepatitis C Infection* and *Requests for Advice Regarding CDEC Recommendations for Hepatitis C Drugs*, and then examined again when newer treatments, such as velpatasvir, Zepatier, and Technivie, are approved and are in use in Canada.

We support the CDEC's first recommendation listed in *Requests for Advice Regarding CDEC Recommendations for Hepatitis C Drugs* and believe that it is important as allowing patients to access treatment sooner would:

- Lessen the emotional, physical, and mental strain on patients and their support communities that comes with waiting to get sicker to access treatment.
  - Many emails PHCN receives about treatment are wondering about health deterioration, wondering if their health deterioration now may allow them to access treatment or allow them to waive BC PharmaCare's liver fibrosis stage F2 requirement.
- Result in better treatment outcomes, even when shorter treatment regimes are prescribed.
  - Clinical trial results show that treatment is more successful when treating healthier patients (resource http://www.journal-of-hepatology.eu/article/S0168-8278%2816%2900086-6/pdf)
  - Over time more is being learnt about the current hep C treatments and their limitations or possible harmful side effects when patients with liver damage take them. The treatments Galexos and Holkira Pak, for example, have been found to possibly be harmful to patients with moderate or severe liver damage.

For recommendations 3 and 4, we would encourage more research into treatments for genotypes 4, 5, and 6, and would support this topic being addressed again at a later date when additional treatments are approved for use in Canada.

Requested Input into the use of Ribavirin (RBV) in Treatments for Hepatitis C

When asked what their thoughts were about treatments combined with ribavirin, those with hep C and those who support those with hep C said that after learning about ribavirin, its potential side effects and benefits, they viewed ribavirin as a necessary evil that can increase a treatment's chances of success. Also, they indicated that they view ribavirin with less concern than they do pegylated interferon or treatments possibly requiring pegylated interferon.