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Dear Ms. Chuly,

We were very pleased that Pharmacare and the Minister of Health announced its decision on June 12, 2003, to provide Pegatron to persons infected with hepatitis C in British Columbia. As you know, BC was the last province in Canada to make this drug available to patients, in spite of its substantially enhanced efficacy over the previously available Rebetron.

We were, however, alarmed by the criteria which have been set for accessing this drug. It is our understanding that the inclusion and exclusion criteria for accessing Pegatron are as follows:

Inclusion Criteria

- hepatitis C treatment naïve
- ALT >1.5 ULN on two consecutive occasions at least 3 months apart
- GT 1, 4, 5, 6: >2 log reduction in HCV RNA by week 14 (if yes, additional 34 weeks coverage)
- GT 2, 3: maximum period of coverage is 24 weeks

Exclusion Criteria

- aged less than 18 years
- decompensated liver disease
- active alcohol abuse
- higher risk of non-compliance
- pregnancy or lack of appropriate contraception
- illicit IV drug and/or intranasal cocaine use

Our primary concern is that these criteria are not based on currently available scientific evidence from the medical literature.

For your convenience, we are providing an outline of the evidence that we hope will provide the basis upon which the criteria will be changed. As they are, the criteria place undue and unnecessary limitations on accessing what for many may be a life-saving drug.

Treatment Naïve

This criteria is presumably based on the thinking that people who have tried and failed previous hepatitis C treatment stand little chance of succeeding with Pegetron. However, the evidence clearly indicates that the issue is not nearly so simple.

Not all people who have taken hepatitis C treatment and have not achieved a sustained virologic response (SVR – what is considered the gold standard of success of Hepatitis C treatment) are alike. There are non-responders (people whose virus didn't respond to treatment), relapsers (people whose virus did respond but once treatment ended the virus came back), and breakthroughs (people whose virus responded but came back while still on treatment). These groups have very different response rates upon re-treatment, contingent on a variety of factors, including what they were initially treated with [1].

Non-Responders:

Within non-responders, there are the people whose virus didn't respond at all to therapy, and there are those whose virus decreased at least two logs but remained detectable. The latter group may have significant improvements in their ALT and hepatic histology; they may also have improved response to more efficacious treatment [2, 3].

Most data on the re-treatment of non-responders is based on standard interferon (IFN) treatment (with or without ribavirin). Whether people took interferon monotherapy or Rebetron (i.e. combination interferon and ribavirin) has a significant impact as to whether their virus will respond to pegylated interferon [1].

Among non-responding people who were *re-treated with regular interferon (IFN) and ribavirin (RBV)*:

- From meta-analyses, it was found that *among non-responders to IFN monotherapy* when retreated with IFN+RBV, 26-32% became HCV RNA negative, and an average of 15% achieved a SVR [1].

When re-treated with pegylated interferon plus ribavirin:

- A study of 17 non-responders to IFN-monotherapy and 84 non-responders to IFN+RBV, all having genotype (GT) 1, found 25-40% of people achieved a SVR with PEG+RBV (only 10-11% among people who had previously not responded to IFN+RBV) [4]
- In a study of 212 non-responders to either IFN-mono or IFN/RBV combination, retreated with PEG+RBV, all with advanced fibrosis or

cirrhosis, and 88% GT1: among IFN-monotherapy non-responders, 53% responded to re-treatment, and 34% achieved a SVR; among non-responders to IFN/RBV, 30% became HCV RNA negative, and 11% achieved a SVR. SVR occurred in 15% of patients with GT1, and 60% of GT2/3. Only 11% of African-Americans became HCV RNA negative during retreatment, none achieved SVR [5].

Presentations at Digestive Disease Week 2003:

- Among 219 individuals, some IFN-monotherapy non-responders, some IFN/RBV non-responders; some IFN/RBV relapsers; SVR for relapsers was 42%, for combination therapy non-responders, 8%; for mono-therapy non-responders, 21% [6]
- Non-responders re-treated with Peg+RBV [6],
 - SVR in all GT: 15%
 - SVR in GT1: 5-9%
 - SVR in GT 2/3: 13-25%
- In an on-going study of 439 non responders to IFN with or without RBV, the end of treatment response (ETR) so far is 46% and SVR was 33%; SVR higher in GT-non 1 and those who previously failed IFN mono-therapy; SVR in GT1 pre-treated with IFN/RBV was 15% [7]
- Among 193 non-responders to IFN+RBV, treated with PEG+RBV, there were improvements in inflammation (as measured by HAI), but not fibrosis (most improvements seen in those who became HCV RNA negative); SVR was 9% [8]
- Brazilian study presented at the Annual meeting of the European Association for the Study of the Liver (2003) found that among 131 individuals who had been treated for at least 6 mths with Rebetron found upon treatment with PEG/RBV at 24 weeks, 89% of relapsers and 67% of non-responders became HCV RNA negative, and after 48 weeks of treatment, 80% of relapsers and 58% of non-responders were HCV RNA negative [9].

Relapsers:

- *Re-treated with IFN mono vs. IFN/RBV for 24 weeks* [10]
 - 49% of relapsers treated with IFN mono became HCV RNA negative, and 5% had SVR
 - 82% of relapsers treated with IFN/RBV became HCV RNA negative, and 47% achieved SVR
- *Re-treated with PEG/RBV* [4]:
 - 87% achieved EOT response, and 60% SVR

ALT Levels:

One of the key criteria for accessing Pegetron is persistently elevated ALT levels. ALT levels are well known to be poor correlates of disease progression [11]. Based on a study of 867 patients, among those with persistently normal ALT values, 65% had a METAVIR score of at least F1, indicating at least some liver fibrosis (PPV=99%, NPV=35%) [12]. Furthermore, factors that may affect ALT levels are HLA class, sex, and body mass index [12], all suggesting that ALT levels are a poor marker of disease. Alarming reports in the community indicate that some individuals are so desperate to elevate their ALT's in order to access Pegetron that they are consuming large quantities of alcohol before having blood drawn.

It is also important to note that people with chronic hepatitis C infection are more likely to achieve a sustained virologic response if there is no fibrosis or cirrhosis [11]. This would suggest that early treatment is better, and that individuals should not wait until their liver is inflamed or diseased before taking treatment.

Stopping Rules:

It is very important for policy-makers to consider that although a sustained virologic response is the gold standard of effective hepatitis C treatment, from the patient's perspective the key issue is to a) maintain liver function, and b) to improve liver function even if there is still virus present. There are many new treatments and therapeutic vaccines for hepatitis C in development, and for patients currently infected with hepatitis C, if the goal of a sustained virologic response is not possible, then keeping one's liver functioning until there are more effective treatments available becomes the goal. There is research that indicates that in spite of a lack of virologic response, histologic response is achievable using "maintenance therapy". The concept of maintenance therapy is based on the observation that up to 40% of non-responders have a histologic response during treatment [2, 3].

In a meta-analysis examining histologic improvements following PEG/RBV treatment, Poynard et al. found [13]:

Treatment Response	Number	Fibrosis Improved	Fibrosis Stabilized	Fibrosis Worsened
Sustained	1094	25%	68%	7%

responders				
Relapsers	464	16%	67%	17%
Non-responders	1452	17%	62%	21%

Another important consideration regarding the stopping rules for Pegetron is that people co-infected with HIV may have altered HCV viral dynamics in response to HCV treatment and may therefore require a longer period to reach >2 log reduction in HCV RNA [14].

Pegetron in children:

One of the exclusion criteria is if patients are aged less than 18 years. Although data are limited on the use of pegylated interferon in children, a small study of 14 children, of whom 13 were GT1, who were all treated with PEG monotherapy, found that at 72 weeks 42% achieved a SVR. [15]

Other Exclusion Criteria:

Active alcohol abuse, higher risk of non-compliance, pregnancy or lack of appropriate contraception, illicit IV drug and/or intranasal cocaine use are all listed as exclusion criteria. However, none of these issues are defined. What constitutes alcohol abuse? What is ‘appropriate contraception’? Is the illicit IV drug and/or intranasal cocaine use based on ever having used, or currently using? And while the reason behind the latter criteria is presumably to prevent re-infection, what if an individual only uses sterile paraphernalia?

Management of Ribavirin Toxicities:

An important and thus far completely neglected issue by Pharmicare in relation to treatment of hepatitis C infection, are the hematologic toxicities associated with ribavirin treatment, specifically anemia. These result in discontinuation of treatment in 10 to 14% of patients [11], and the reduction of ribavirin dose (resulting in poorer response rates) among many, many more. There are few treatments available for the treatment of ribavirin induced anemia. However, Eprex (epoetin-alfa) is a licensed glycoprotein product manufactured using recombinant DNA technology. It contains the identical amino acid sequence of isolated natural erythropoietin, and is indicated for use in patients with kidney failure, surgery patients, cancer patients (because both cancer itself and

chemotherapeutic agents can induce anemia), as well as zidovudine induced anemia in patients with HIV infection. Although not well studied in the setting of ribavirin induced anemia, a preliminary study found that 88% (vs. 60% on placebo, $p < 0.001$) of patients who received the recombinant epoetin-alfa were able to maintain full dose ribavirin therapy, and that quality of life measures were much higher in the Eprex treated group compared to placebo [16].

In summary, we feel that given existing data, the criteria for accessing Pegatron in British Columbia are lacking in a number of important ways that have direct impact on patient's lives. While we understand the need to contain costs, this need must be balanced against the medical needs of people struggling against chronic hepatitis C infection. Hepatitis C treatment is not a life-long treatment. The lifetime costs, however, of chronic hepatitis C disease are substantial if one considers the costs of hospitalization, health care utilization, and transplantation. The BC Center for Disease Control has estimated that the medical costs without treatment for a person with hepatitis C, from diagnosis to death, are approximately \$1 million [17]. This is compared to the approximately \$11,000 for a 32-week course of Pegatron.

We strongly urge you to consider the data we have presented to you, and to conduct your own research on these issues. We are confident that you will agree that the science does not support the criteria, and we eagerly await your response.

Sincerely, on behalf of the BC HIV/Hepatitis C Co-Infection Action Coalition,

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