HEALTH TECHNOLOGY APPRAISAL ASSESSMENT REPORT PEGINTERFERON ALFA AND RIBAVARIN FOR THE TREATMENT OF CHRONIC HEPATITIS C (PART REVIEW OF TA75 AND TA106)	
TO:NICE	**FROM: NHS QUALITY IMPROVEMENT SCOTLAND 10 FEBRUARY 2010**

I am specifically asked to comment on whether there were any differences in the epidemiology or treatment pathways within Scotland that would change the interpretation of this assessment report. There are not and for these issues Scotland could be regarded in the same light as England although of course the pathway of implementation, if any, of these recommendations would be different given the hepatitis C Action Plan.

In terms of the report itself, this is a particularly poor report. The objectives of the report were to assess the clinical effectiveness and the cost effectiveness of treatment with pegylated interferon and ribavirin for three specific subgroups of patients – those eligible for short course treatment, those who had previously failed treatment and those who were co-infected with hepatitis C and HIV. The report only draws a conclusion on the cost-effectiveness of short course treatments and makes no comments on the other five points that it was intended to respond to. It correctly points out the limitations of the available data on these six topics, but it discounts valid conclusions and results from some studies on the grounds that the studies don't fit methodological criteria that they had specified where these criteria are unlikely to affect the result of the study. The result is that they are unable to come to clinically meaningful conclusions. From the current Scottish care pathways perspective, patients who are co-infected with HIV and hepatitis C would be offered interferon and ribavirin therapy and this would be regarded as a clinically effective and cost effective therapy.

With regard to re-treatment of patients who previously relapsed or failed therapy, care pathways currently would only offer this to highly selected patients who had a good indication that treatment had been suboptimal on the first occasion and that the outcome would be better on a second. I don't think the NICE recommendations would change this practice in Scotland.
With regard to short course treatments, these have not yet been widely established in Scotland.

A few centres are using them in highly specified patient groups, but most clinicians would agree that there is a paucity of good evidence for shortening treatment in most patients. The evidence is best around those patients with genotype 1 who have a low viral load and a rapid virological response which occurs in only 25% of patients with hepatitis C genotype 1 which represents about 50% of the infected population in Scotland and short course therapy for genotype 2 which represents less than 5% of the infected people in Scotland.

[redacted]

10 February 2010

I have been asked to comment specifically on whether there are differences in the epidemiology and current treatment pathways for HCV infection in Scotland which would suggest that the evidence presented in this report would differ in its applicability to the rest of the UK.

Overall, the epidemiological characteristics presented in the assessment report are comparable to those in Scotland. For example, the following epidemiological characteristics detailed within the report also apply to Scotland:

- "In England and Wales, the most prevalent genotypes are 1 and 3, representing more than 90% of all diagnosed infections" (page 17)
- "The most common source of HCV transmission in the UK is through the sharing of injecting paraphernalia during illicit intravenous drug use, accounting for around 90% of cases" (page 17)
- "It is estimated that around 40% of IDUs are infected with chronic HCV" (page 18)
- "It is suggested that up to 10% of all HCV infected people are co-infected with HIV" (page 19)

The following epidemiological characteristics detailed in the report for England differ from those in Scotland, but these differences would not impact on the findings of the economic analyses and conclusions:

- Regarding "In England & Wales the HPA estimate that …. 142,000 people chronically infected; a prevalence of 0.44% (95% CrI 0.29-0.72) in this age group [15-59 years]" (page 18). This compares to an estimated 39,000 people living in Scotland who were chronically infected with HCV in 2008 (see Hepatitis C in the UK 2009 Report: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1259152221464); and thus represents a higher prevalence in Scotland (0.75% among all ages) compared to England & Wales (0.44% among those aged 15-59 years).
- Regarding "Between 1992 and 2007 there were 62,000 laboratory confirmed diagnoses of HCV in England" (page 19). This represents an under-estimate of diagnosed infection in England because of sub-optimal reporting of confirmed diagnoses to HPA in England. In Scotland, the completeness of laboratory data on HCV diagnosed persons is high, with an equivalent 24,000 laboratory confirmed diagnoses of HCV during 1991-2007.

The treatment pathway for HCV presented in the assessment report would appear to be comparable to that in Scotland, although there is very little detail regarding how SHTAC have dealt with the issue of liver biopsy in their economic analysis. The authors only mention that "Protocols describing the frequency and intensity of monitoring of patients being treated with peginterferon were developed for the previous assessment, based on clinical guidelines and discussion with hepatologists/specialist nurses at Southampton University Hospitals Trust, and are described in full in the previous assessment report" (page 105). Thus, a reader can only fully appreciate the methods applied from further scrutiny of the previous HTA report. From review of the previous HTA report (by Shepherd J, et al. HTA 2007; 11: 1-205), it states that "those patients suitable for therapy …… will be admitted as a day case for a liver biopsy prior to the start of treatment" (page 69); further it states that "reducing the cost of liver biopsy improves the cost-effectiveness of the watchful waiting strategy. Biopsy is assumed to be the

surveillance mechanism for monitoring patients' disease progression and determining eligibility for treatment under watchful waiting" (page 81). The treatment pathway, involving liver biopsy, described here is not in line with the SIGN (Scottish Intercollegiate Guidelines Network) National Clinical guideline on the management of Hepatitis C; this states that:

- "Liver biopsy should be performed if there is concern about additional causes of liver disease"
- "Repeat liver biopsies should be considered in patients with mild disease who remain untreated, if progression of liver fibrosis would influence the decision to opt for antiviral therapy"
- "Liver biopsy should not be considered an essential test prior to using antiviral therapy, especially in patients with genotype 2 and 3 disease".

In the previous HTA report (by Shepherd J et al), the authors have undertaken some sensitivity analyses to assess the impact of liver biopsy on cost-effectiveness, but the current assessment report does not undertake any sensitivity analysis in relation to the role of liver biopsy and thus is a limitation in terms of applicability to the whole of the UK, where practice is known to vary in this respect.

Additional comments of note:

- Regarding "It is estimated that 6 to 10% of cirrhotic patients will progress to decompensated cirrhosis" – this must relate to an annual rate.
- Regarding the "Additional analyses undertaken by SHTAC" (page 77), it is unclear what changes to the manufacturer's model have been made and to what extent the issues raised on pages 76-77 have been addressed.
- Regarding "Individuals in this health state [SVR state] are assumed to face the same mortality risks as the general population" (p 101). This is an under-estimate of the non-HCV-related mortality risk among the population who have chronic HCV, as the vast majority of these individuals have ever injected and reside in the most deprived parts of the UK and thus have a higher risk of mortality than the general population. This is a factor which has not been taken into account or acknowledged in the report.

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Responses based on questions in Appendix A

Is it appropriate to limit?	Yes
Are the populations defined appropriately ?	Yes
Are there any subgroups?	Difficult to answer: see later
Rx of hep c in children?	Not qualified to answer

The issues appear to be the new licenses approved for

1) shortened Rx duration for G1 with LVL and RVR, G4 with RVR both from 48 to 24 weeks and for non G1/4 with RVR from 24 to 16 weeks: This is different from SMC advice and whilst the data is interesting, the numbers

really are very small and I would be wary of extrapolating on the basis of these to any major change in current practice. Scottish guidelines support the potential reduction for patients with G1/4 with RVR and LVL but not for G2/3 with RVR.

2) I cannot see a compelling reason to switch NICE advice on current info, but this should be reviewed as and when there is data covering a larger patient group as the reduced side effects and reduced costs are obviously attractive to the nhs and the patients. Some may advocate a large nationwide trail looking at this in 2-3 regions to get these answers faster if there is nothing coming over the horizon from the drug companies?

3) Re Rx of non responders/relapsers to prev Rx with peg and non peg combination and monotherapy. Current SMC guidance advocates re Rx with either pegasys or viraferon peg and ribavirin for all those who have been non-responders or relapsed after Rx with pegylated or non pegylated interferon with or without ribavirin. The SMC data shows 8, 15 and 23 % SVR after 48,72 and 48 weeks combination therapy in these groups of almost all G1 patients with significant costs but 'reasonable costs per QALYs. This NICE data TA 75/106 also has good data and reasonable £/QALY particularly when stopping re Rx if no EVR at week 12 9non responders to re Rx). The data presented supports the extension of the licenses to re Rx these cohorts of patients under NICE guidance.

4) Rx of co-infected HCV/HIV: The HIV/HCV world has changes with the improved outcomes from the use of HAART and the data assessed here in TA75/106 makes compelling reason with good clinical and cost effectiveness. The data supports the extension of licensing to Rx co-infected HCV/HIV patients under NICE guidance.

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