APPENDIX E

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Health Technology Appraisal

Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C – part review of Guidance #75

Response to consultee and commentator comments on the draft scope

Consultee	**Subject in Scope**	**Comment**	Response
SHTAC (AG)	Title Appraisal objectives	The title refers to non-pegylated interferon alfa, yet pegylated interferon is included as an intervention. It would be better to amend the title to 'Pegylated interferon alfa and ribavrin /Interferon alfa and ribavirin for the treatment of… The scope needs to be clearer as to whether the appraisal only covers patients with mild HCV, or whether it will also include an update of the evidence relating to patients with moderate to severe HCV. We have forwarded separately trial evidence for the effectiveness of pegylated interferon and ribavirin in this patient group published since our previous assessment report. From a brief reading of these it appears that none of them would necessarily influence the current guidance.	Change title to interferon (peg or non-peg) + ribavirin to reflect what the Committee wish to do. A sentence and clause added to the section to make the intention clearer.
DoH	Background	The Department of Health's guidance to the NHS uses a figure of 20%-40% for viral clearance at the acute stage, and 5-20% (of those with chronic infection) for progression to cirrhosis after 20 years – see Hepatitis C: Essential information for professionals and guidance on testing, http://www.hepc.nhs.uk/resources/documents/HepC_Information.pdf. Would you consider reflecting this information in the scope? …would like to propose a definition of "mild" hepatitis C disease as follows:	The scope was amended following the comments made by the consultee. The scope was

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Roche		"a necro-inflammatory score of less or equal to 3 / 18 and a fibrosis score of less than or equal to 2 / 6".	amended following the comments made by the consultee.
SHTAC Roche	Technology	Under 'The technology' it should be pointed out that the licensed indication for Pegasys has changed so that histologically proven CHC is no longer a requirement for patients with genotypes 2 and 3. Pegylated interferon alfa 2a (Pegasys) is currently indicated for the treatment of chronic hepatitis C in adult patients who are positive for serum HCV-RNA, including patients with compensated cirrhosis. This licensed indication therefore presently includes the treatment of mild hepatitis C patients. Pegylated interferon alfa-2a has also recently received EMEA approval for use in patients with normal ALTs.	The scope was amended following the comments made by the consultee The scope was amended following the comments made by the consultee, as for SHTAC above.
SHTAC	Interventions	With regard to the question raised on page 3 as to whether or not non-pegylated interferon alfa should be included in the appraisal (given that pegylated interferon is now the gold standard treatment for patients with moderate to severe HCV) there are arguments for and against. If current practice is not to treat patients with mild disease but to watch and wait, and if it can be assumed that if clinicians were to treat they would likely choose pegylated interferon, then the appropriate comparator would be pegylated interferon versus no treatment / watchful waiting (NB. the as yet unpublished multi-national trial by Zeuzem *et al.* which compares pegylated interferon alfa-2a with no treatment would likely be eligible in this assessment). It would also mean that including non-pegylated interferon alfa as an intervention in the appraisal would be less relevant, given that it would be unlikely to be used in practice. If it were to be included, however, a potentially eligible study for assessment would be the HTA funded RCT of interferon alfa and ribavirin in patients with mild HCV. This trial was conducted in 13 centres around the UK and has the added advantage of an assessment of health related quality of life	The scope was amended following the comments made by the consultee in at least 2 ways: change in title, and adding non-pegIFN as an intervention

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Roche		(HRQOL), and cost-effectiveness analysis. Since HRQOL may be a key factor in the decision to treat patients with mild disease, primary data on the impact on HRQOL of anti-viral treatment is therefore important. This study appears to be the only published trial (identified at the current time) providing HRQOL data for patients with mild HCV (NB. It is not clear whether the Zeuzem *et al* trial assessed HRQOL as an outcome). The other advantage of this trial is that it has reported data on costs and consequences from a UK perspective, and will therefore be particularly relevant to an assessment applicable to England and Wales. Since pegylated interferon alfa 2a (40KD) and pegylated interferon alfa 2b (12KD) have different costs and dosing schedules, we suggest that the interventions be listed separately. Professor Thomas's trial utilises "conventional interferon", whereas the intervention in the scoping document is described as "pegylated interferon". Therefore, we would like to clarify with you our assumption that Professor Thomas's trial will be utilised to inform the efficacy of the comparator arm only	This is a matter for the appraisal rather than the scope. Prof Thomas' trial will be used both as an intervention (against no treatment) and in modelling, as a comparator (against pegIFN + ribavirin)
Hep C Trust	Population	we think it important that Prof Zeuzem's recent study of the treatment of people with normal ALT levels should be considered, even though he found significant liver damage in around 30% of those enrolled.	"Other considerations" ensures that the Zeuzem trial will be used to inform about people with mild

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			CHC.
SHTAC	Current standard treatment	We note that 'Best standard care with and without interferon' is reported as a 'standard'. Is this taken to be the comparator intervention? To our knowledge there have been no head-to-head comparisons of non-pegylated interferon alfa and pegylated interferon alfa in patients with mild HCV (although a recent US cost-effectiveness analysis indirectly compared pegylated interferon with non-pegylated interferon in patients with raised ALT levels but without evidence of fibrosis on biopsy).	The scope was amended by adding "as evidence allows" and to make clear under "modelling" that pegIFN comb therapy should be compared with IFN comb therapy as well as both peg and non-peg IFN against best supportive care
DoH		**page 2, 3rd row of table - Standard:** Should interferon read 'ribavirin'?	Not ribavirin. Clearer statement of comparator should clear up the matter.
Roche		We believe that best standard care requires some form of definition. For simplicity, it will be most practical to utilise "no treatment" and "conventional interferon" as current standard comparators.	The scope was amended following the comments made by the consultee.
SHTAC	Outcomes	1 Are these listed in any order of priority? 2 Suggest that sustained virological response is listed before virological response (end of treatment) as this is a 'harder' outcome. 3 Add ALT levels? 4 Mortality - this unlikely to have been measured in RCTs. Consideration of	The scope was amended following the comments made by the consultee

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Roche		modelling methods to consider the long term consequences will therefore be necessary. We would recommend that sustained virological response should be broken down further to include virological response at 12 weeks.	The scope was amended following the comments made by the consultee
Haemophilia Society	Other considerations	An additional subgroup that should be covered is those with mild CHC and HIV co-infection.	The scope was amended following the comments made by the consultee
Roche		Conventional interferon should also be included in the review, even though the current hepatitis C guidance recommends the use of pegylated interferon. This is because conventional interferon has not previously been compared to pegylated interferon in this setting (i.e. mild disease).	The scope was amended following the comments made by the consultee
		No Phase III randomised control trial has yet been performed using pegylated interferon in exclusively "mild" hepatitis C patients. The pivotal registration trials for pegylated interferon alfa 2a were performed in a cohort of hepatitis C patients with a wide variety of histology. Therefore, in order to evaluate the clinical and cost effectiveness of pegylated interferon alfa 2a in "mild" patients, Roche proposes to undertake a sub-group analysis of the relevant trials. This would be in addition to analyses of the two new studies referred to in the draft scoping document. Roche therefore expects to use multi-variate analysis to elicit treatment effects from the pivotal trials as necessary.	The scope was amended following the comments made by the consultee (a) to include in the trials people with CHC and normal ALT levels and (b) a new clause under "other considerations"

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Hep C Trust	General comments	We believe that non-pegylated interferon *should* be included because there may not be sufficient evidence from trials of pegylated interferon alone. However, we believe it should be included *as evidence only* and no guidance should be issued on its use, because we are concerned that PCTs should not be given the opportunity to fund non-pegylated interferon instead of pegylated interferon *under any circumstances.* As patient representatives our focus is much more on what is clinically effective than on what is cost effective and numerous trials have demonstrated that pegylated interferon is, to varying degrees, significantly more clinically effective than non-pegylated interferon, albeit in the treatment of moderate to severe chronic hepatitis C. Given the chemistry involve, it is difficult to see that non-pegylated interferon will emerge as more clinically effective for mild disease than pegylated interferon but there might be enough evidence to recommend non-pegylated interferon and not enough for a judgement on pegylated interferon. However, patients with mild disease but with symptoms of extra-hepatic HCV infection sufficient to impair the quality of life may be treated with pegylated interferon under existing guidance. We feel therefore that to offer often cash-strapped PCTs the opportunity to provide the cheaper non-pegylated interferon would be a step back for patients. 1 Non-pegylated interferon • This should only be included in the review in the unlikely event of the review of the results of clinical trials show it to be significantly superior to pegylated interferon.	The rationale for including conventional IFN as an intervention was made clearer, following the comments made by the consultee, and because it follows from the Committee's wishes expressed in Guidance #75.
Haemophilia Society		2 Some consideration needs to be given to the assessment of mild hepatitis C in those people who are being managed without liver histology. The group would like to recommend on ground of harmreduction to open up the existing guidance on the treatment of Hep C with peg interferon and ribavirin and to	Covered by response to other consultees

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RCGPs Sex Drugs and HIV Group		be specially openminded to treating current i.v. users as this might be helpful in two ways: a) harmreduction b) another opportunity to motivate people to engage in treatment for their substance misuse problem.Also looking at the costs of the difficulties in obtaining a liver transplant it seems more sensible to prevent further progression of liver disease through earlier intervention particularly in genotype 2 and 3 which have better outcomes then to wait until permanent damage has been done. Comments (pdf) are précised: does not want non-peg IFN as a comparator (various reasons).	Covered by response to other consultees. The topic of i.v. drug users is already in the scope in this section. On costs, a full economic evaluation should include the possibility of transition to liver transplant.
Institute of Hepatology		NICE reply: Dear Prof Williams, I thought that I should send you a quick note about your comment on the draft scope for Hep C, in which you suggested strongly that the Appraisal Committee should not consider evidence about IFN + ribavirin combination therapy. The reason the draft scope was written that way was to allow inclusion of Howard Thomas's trial, which was of IFN + ribavirin for mild hep C, not pegIFN + ribavirin. The intention was to increase the evidence base rather than to revert to IFN therapy for this group. Seen in this light, would you be happy for us to proceed with the inclusion of IFN as a therapy so as to allow the Thomas trial to be considered in the evidence base? The additional salient features of this work are (a) HRQoL is available for consideration on a before and after basis for those for whom the virus has been cleared and those for which it has not, and (b) it has an associated cost-effectiveness analysis which extrapolates to combination Peg therapy, showing it to be cost effective to treat mild genotypes 2/3 with Peg combination over IFN combination and therefore obviating the need for biopsy in this group of patients. It would seem to be a pity if this evidence were placed outside the scope of the	Matter cleared up by correspondence (reproduced in the Comment column), although the grounds stated in the letter for inclusion of IFN therapy in the appraisal have changed to reflect closer adherence to the Appraisal

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		appraisal. Yours sincerely Alastair Fischer, PhD Prof Williams reply: Dear Dr.Fischer, Thank you for your letter and with the further information you have given me I am happy for IFN to be included, on the basis of its trial in mild HCV disease. Yours sincerely, Roger Williams	Committee's wishes: no further action.

Statement of 'no comment':

- British Nurses Liver Forum
- Welsh Assembly Government
- Haemophilia Alliance
- NHS Quality Improvement Scotland
- Royal Pharmaceutical Society
- Transplant Support Network
- Welsh Assoc of Renal Physicians and Surgeons