NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C (part review of technology appraisal guidance 75 and 106)

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Roche Products	**1.** Has all of the relevant evidence been taken into account? Roche is not aware of any other data that would assist the Committee in addressing the decision problem for this appraisal. Roche believe that high quality RCT data should be used to appropriately guide clinical practice. **2.** Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? In the main Roche believes that appropriate interpretation of the evidence is documented throughout the ACD in relation to the three decision problems. There are 2 areas relating to interpretation that we would like to provide comment on: 4.1.12 – Summary of clinical effectiveness evidence Roche feels that it would be appropriate to highlight that shortening the treatment duration for genotype 2 & 3 patients is only indicated for peginterferon alfa-2a. 4.2.23 – ICERs for retreatment Roche feels that this paragraph should emphasise the point that the ICERs for peginterferon alfa 2b is a blended calculation for relapsers & non responders, whereas the ICERs for peginterferon alfa-2a focus on non responders, therefore the calculations are not interchangeable/comparable.	Comments noted. No action required. Comment noted. This information is included in the FAD in sections 3.8, 4.1.1 and 4.1.12. Comment noted. This information is included in the FAD in section 4.2.24 as follows:" The ICER for the subgroup of people who had been treated previously with peginterferon alfa-2b plus ribavirin or peginterferon monotherapy **but whose hepatitis C did not respond to treatment, or responded initially to treatment but subsequently relapsed**, was £23,912 per QALY gained (compared with best supportive care) for people with HCV genotypes 1 and 4." and "Re-treatment with peginterferon alfa-2a plus ribavirin of people **whose hepatitis C did not respond to previous peginterferon** therapy resulted in an ICER of £52,587 per QALY gained for people with HCV genotype 1and £10,926 per QALY gained for people with other genotypes, each

	3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS? Yes, Roche welcomes the positive endorsement this ACD provides in ensuring that high clinical need can be met in the challenging areas of HIV/HCV co-infection and the treatment of prior non responders & relapsers. The decision to offer shorter treatment duration is also welcome. **4.** Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? Roche has supported the social & health equality focus of previous guidance (TA075 & TA106) which has explicitly stated the extension of guidance to people who continue to misuse alcohol and/or use intravenous drugs. It could be a useful addition to this new guidance if this recommendation could be included.	compared with best supportive care." Comment noted. No action required. Comment noted. Specific recommendations for people who continue to misuse alcohol and/or intravenous drugs were not contained in previous guidance (TA75 and 106). The Committee considered that these factors should be taken into account by prescribing clinicians. The Committee considered that this guidance updates and replaces: • section 1.2, bullet 3 only, of TA75 • section 1.4 of TA75 for adults who are eligible for shortened courses of combination therapy (as described in section 1.2 of the current guidance) • section 1.7, bullet 1 only, of TA75 • sections 1.4 and 1.5 of TA106. All other recommendations in TA75 and TA106 still stand. In light of this, the Committee concluded that a specific statement on this issue in this appraisal was not required.
Schering-Plough	MSD welcomes this opportunity to respond to the Appraisal Consultation Document. Overall we are pleased with the preliminary guidance, and are confident that the ACD reflects the best interests of patients and the NHS in ensuring treatment choice and appropriate use of peginterferon and ribavirin. On this basis, it is our view that the provisional recommendations are sound and constitute a suitable basis for the preparation of guidance to the NHS.	Comment noted. No action required.

	MSD is confident that the relevant comparators have been taken account and that the summaries of clinical and cost effectiveness are accurate. MSD is not aware of any aspects of the recommendations which would need particular consideration to ensure that unlawful discrimination does not takes place.	

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Royal College of Nursing	**1**. Has the relevant evidence has been taken into account? The evidence considered seems comprehensive.	 Comment noted. No action required.
	2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate? These seem reasonable and appropriate.	 Comment noted. No action required.
	3. Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? Nurses working in this area of health have reviewed the recommendations of the Appraisal Committee. The provisional recommendations seem a suitable basis for guidance to the NHS. There are no further comments to add to the document at this stage. The RCN would welcome guidance to the NHS on the part review of the existing guidance on the use of this health technology.	 Comment noted. No action required.
	4. Are there any equality related issues that need special consideration that are not covered in the ACD? None that we are aware of at this stage. We would however, ask that any guidance issued should show that equality issues have been considered and that the guidance demonstrates an understanding of issues concerning patients' age, faith, race, gender, disability, cultural and sexuality where appropriate.	 Comment noted. No issues concerning equality were identified during the scoping exercise or during the course of this appraisal.

Nominating organisation	Comment	Response
Royal College of Pathologist	1) This report analyses the evidence relating to shortened courses of therapy for HCV infection. All published studies utilise both pre-treatment viral load (classified as high or low, with actual values given) plus an assessment of response to therapy at 4 weeks to underpin the decision whether or not to shorten the period of therapy for a particular patient. Patients achieving an undetectable viral load at 4 weeks are eligible for consideration of shortened duration therapy. However, nowhere in this document (at least that I could find) is there a useful definition of an undetectable viral load. This is a serious deficiency. "Undetectable" is an entirely flexible concept, being dependent on the sensitivity of the assay used. Lower limits of detection in various commercially available HCV viral load assays vary from as low as 12 iu/ml (e.g. Abbott 2000) through to 615 iu/ml (bDNA assays) i.e. by as much as 1 log! The consequences of not giving any guidance at all on a defining level of undetectability will be that practice (and therefore presumably clinical outcomes) will vary between different hospitals and clinics, dependent on which particular assay the serving virology laboratory happens to use. I can appreciate that it may be difficult to give a hard and fast rule on what constitutes undetectability, and that the various clinical trials of shortened therapy may have used different assays with different lower limits of detection. However, it should not be beyond the scope of the experts involved in drawing up this report to make a recommendation, based on what evidence there is, even if this is made with a qualifying statement of some sort or other. At the very least, the lower limits of detection used in the clinical trials that form the basis of this report should be stated, so that readers have some "ball park" guidance. My own preference would be to see a definition of undetectability as being less than 30 iu/ml.	Comment noted. The Committee discussed the range of limits defining 'undetectable' virus in the evidence from clinical trials underpinning this appraisal and acknowledged that different laboratories in the UK use different tests and set different thresholds to determine whether a virus is undetectable, and that the quality of the test used may influence treatment decisions. The Committee therefore agreed that a highly sensitive test should be used to detect serum HCV RNA, to minimise the chance of false negative results. See FAD sections 4.1.3 and 4.3.6.
	2) Page 11, para 3.12. The costs of 48 weeks of therapy with PEG-alpha-2b + RV are double the costs of 24 weeks of therapy, which is what I would expect. Why then, is the cost of 48 weeks of PEG-alpha-2a + RV (£11,425) considerably more than double the cost of 24 weeks of therapy (£4824). Is there an error in here somewhere?	Comment noted. The cost of 48 weeks of peginterferon alfa-2a plus ribavirin treatment is more than double that of 24 weeks peginterferon alfa-2a plus ribavirin treatment because the dosage of ribavirin is genotype-dependent (and for genotypes 1 and 4 it is also weight-dependent). The cost for 24 weeks of peginterferon alfa-2a plus ribavirin treatment was estimated for people with genotypes 2 or3 whereas the cost for 48 weeks of peginterferon alfa-2a plus ribavirin treatment was estimated for people with genotypes 1 or 4 (as these are the standard treatment durations for people with those genotypes).

Nominating organisation	Comment	Response
NHS Quality Improvement Scotland	**1.** Do you consider that all the relevant evidence has been taken into account? YES. Although, it would be helpful to present the sustained virological response rates, in the Clinical Effectiveness section, for those (i) re-treated after non-response or relapse to pegylated interferon alfa alone or in combination with ribavirin, and (ii) HCV and HIV co-infected, which were thereafter applied in the economic analysis. The relevant evidence has been included. Satisfactory and thorough relevant evidence. **2.** Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence? Yes. On the whole the summaries are fair, with regard to retreatment they have lumped all patients together, the data clearly shows that relapsers with genotype 2/3 have much better responses than genotype 1 non-responders, This should have been reflected in the analysis No. I note the data from TA75/106 and the SMC guidance from 2008 and 2009, along with the committee's views expressed in this recommendation. I remain somewhat concerned that the numbers in the subgroups on which the new guidance is based remain small and the subgroups not always entirely representative. I would prefer a larger study to confirm that there is no significant drop in SVR from the shorter regimes in targeted patients, although I do note the clinical specialist's views that the data could be viewed as clinically comparable. The advice given, (using LVL at Rx initiation and RVR at week 4 to guide which patients from each genotype are candidates for shortened Rx duration), however, is clear, encouraging implementation. **3.** Do you consider that all the relevant evidence has been taken into account? YES. Although, it would be helpful to present the sustained virological response rates, in the Clinical Effectiveness section, for those (i) re-treated after non-response or relapse to pegylated interferon alfa alone or in combination with ribavirin, and (ii) HCV and HIV co-infected, which were thereafter applied in the economic analysis. The relevant evidence has been included. Satisfactory and thorough relevant evidence.	Comment noted. The rates of sustained virological response are provided in the Assessment Report. The FAD includes a summary of the clinical effectiveness data, and does not usually provide this level of detail. Comment noted. The FAD includes a summary of the data on clinical effectiveness provided by the Assessment Group and the manufacturers. Analyses for people whose condition either did not respond to treatment (non-responders) or relapsed following treatment were grouped together in some instances where data were lacking (such as for peginterferon alfa-2b). Comment noted. No action required.

	4. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence?	
	Yes On the whole the summaries are fair, with regard to retreatment they have lumped all patients together, the data clearly shows that relapsers with genotype 2/3 have much better responses than genotype 1 non-responders, This should have been reflected in the analysis	Comment noted. The FAD includes a summary of the data on clinical effectiveness provided by the Assessment Group and the manufacturers. Analyses for people whose condition either did not respond to treatment (non-responders) or relapsed following treatment were grouped together in some instances where data were lacking (such as for peginterferon alfa-2b).
	No. I note the data from TA75/106 and the SMC guidance from 2008 and 2009, along with the committee's views expressed in this recommendation. I remain somewhat concerned that the numbers in the subgroups on which the new guidance is based remain small and the subgroups not always entirely representative. I would prefer a larger study to confirm that there is no significant drop in SVR from the shorter regimes in targeted patients, although I do note the clinical specialist's views that the data could be viewed as clinically comparable. The advice given, (using LVL at Rx initiation and RVR at week 4 to guide which patients from each genotype are candidates for shortened Rx duration), however, is clear, encouraging implementation.	
	I wonder whether, on accepting committee's recommendations, it would be possible to answer my earlier question by analysing our own Scottish numbers with shortened Rx regimes for SVR compared to standard Rx regimes in our populations?	Comment noted. We recommend that you contact the Assessment Group for this appraisal to discuss whether they can assist you analyse your local data using their model.
	5. Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?	
	Yes	
	With the proviso stated in 2 the recommendations are sound	Comment noted. No action required.
	As above (2)	

Southampton Health Technology Assessments Centre (SHTAC)	We feel that the caveats in our report around the fact that SVRs for shortened treatment duration came from relatively small subgroups of the RCTs should be mentioned. The best place would be following on from the last sentence in para 4.1.3, something like "in many of the trials the sustained virological response rates were based on sub-groups of randomised patients who achieved a rapid viral response. It was not reported whether these sub-groups were statistically powered to detect a significant difference between trial arms".	Comment noted. This section has been amended (accordingly, for clarity) – see FAD section 4.1.3.
	Para 4.1.10 - sentence about halfway down "...but these did not meet the inclusion criteria for the review as they featured an active treatment comparator" suggest adding "...but these did not meet the inclusion criteria for the review (based on the decision problem) as they featured an active treatment comparator".	Comment noted. This section has been amended (accordingly, for clarity) – see FAD section 4.1.10.
	4.1.12 - we feel the 1st sentence which reads "...shortening the duration of treatment of peginterferon alfa plus ribavirin to 16 weeks (HCV genotype 2 or 3) or 24 weeks (HCV genotype 1) may be associated with a slight reduction in sustained virological response" is misleading as in some trials shortened treatment was associated with increased SVRs. We would ask that this is removed and replaced with something like "....there are no statistically significant differences between shortened and standard durations of treatment". This same point applies to section 4.3.2 and we would ask that this is similarly amended.	Comment noted. The Appraisal Committee discussed this issue in the second committee meeting and the FAD has been amended to reflect the discussions – see FAD sections 4.1.12, 4.3.2 and 4.3.9.
	Para 4.2.5 - sentence about halfway down "For people whose hepatitis C did not respond or relapsed on previous peginterferon therapy, data on sustained virological response rates were taken from clinical trials" change to "...data on sustained virological response rates were taken from two clinical trials".	Comment noted. This section has been amended– see FAD section 4.2.5
	Section 4.2.9 - 3rd sentence "Although appropriate probability distributions appear to have been used for the probabilistic sensitivity analyses, the Assessment Group noted that limiting the distributions for some inputs does not appear to make best use of data reported in the submission." The bit in bold doesn't actually make any sense and we would suggest changing it to what was said in the report, which was that "...the parameterisation of the distributions used for some inputs does not appear to make best use of data reported in the submission."	Comment noted. In order to make the document as readable as possible to all people, the use of technical language such as “parameterisation” in public documents is avoided. No change to the current wording has been made.
	4.2.21 - the 1st sentence "Data on sustained virological response rates were extracted from clinical trials included in the clinical-effectiveness review and used in the model..." is not quite true. The clinical effectiveness review only supplied SVRs for the shortened treatment duration subgroup of patients. SVRs for the re-treatment and the HCV/HIV subgroups were taken from active comparator RCTs (not systematically reviewed by us).	Comment noted. This section has been amended – see FAD section 4.2.22
	Para 4.3.9 - a cross-reference to section 4.2.22 is given, but should this not be 4.2.23?	Comment noted. This section has been amended– see FAD section 4.3.10 and 4.2.24

Comments received from members of the public

Role*	Section	Comment	Response
Other (David Geffen School of Medicine, University of California, USA)	1	There have been at least 8 randomized trials of alpha-interferon vs no treatment that have assessed clinical outcomes (Valla, Hepatology 199929:1870-5 Mura, Hepatology 199929:A1251 Ikeda, J Hepatol 199828:910-1 Testino, Recenti Prog Med 200293:302-7 Fartoux, Clin Gastroenterol Hepatol 20075:502-7 Di Bisceglie, N Engl J Med 2008359:2429-41 [HALT-C] Hofer, Hepatology 200950:680A (EPIC3) Afdhal, Hepatology 200440:239A [early CO-PILOT report] as well as two using other types of interferon (Bernardinello, Hepatogastroenterology 199946:3216-22 [&#946-interferon] Pockros, Hepatology 2007 45:569-78 [&#947-interferon]) and only one of them has shown a possibly favorable benefit (Mura). Curiously, this trial was published as an abstract in 1999 and, to my knowledge, has never appeared as a final paper. (The other allegedly randomized trial, Nishiguchi, Lancet 1995346:1051-5, has a disproportionately longer followup in the control arm and may not truly have been randomized.) Where is the evidence to justify treatment for anybody? This is particularly the issue since the vast majority of infected patients will never get into trouble even if they are not treated.	Comment noted. The Committee considers all available evidence relevant to the clinical question which is submitted to NICE . This information is retrieved from the published literature by the Assessment Group when determining the clinical and cost-effectiveness of a specific technology. For the purpose of this appraisal, the data available for peginterferon alfa 2a and 2b in the populations under consideration were provided from clinical trials, patient and clinical expert opinions, the Assessment Group's economic analysis, the manufacturer's submissions and responses from consultees and commentators to the Assessment Report. No action required.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
Other (David Geffen School of Medicine, University of California, USA)	2	The endpoints of therapy that are used in hepatitis C treatment trials are surrogate ones that have never been validated. Data that have emerged from the three large long-term treatment trials of patients with severe histologic disease (HALT-C, EPIC3, CO-PILOT) have indicated that the endpoints could improve even though the patients did not, observations that would be incosistent with the surrogates being valid. The focus on sustained viral responses (SVRs) is an incorrect extension of the HIV model. (The vast majority of hepatitis-C infected patients will never get into trouble even if not treated and the serum level of virus may be an epiphenomenon if the virus infects hepatocytes by being in the neighborhood). Since there are prognostic factors for SVRs (little fibrosis, recent infection, female gender, normal weight, etc.), it is incorrect to assume that a 50% SVR rate translates into a 50% reduction in future morbidity. (Many of these factors identify people less likely to get into trouble and disease progression may largely be confined to those who do not respond.) There is insufficiant evidence to recommend treatment based on improvements in these surrogate markers.	Comment noted. The reliability of the available evidence is considered by the Committee when formulating its recommendations. No action required.
Other (David Geffen School of Medicine, University of California, USA)	3	The medications clearly have toxicities, including occasional deaths. They are expensive. Why are we asking patients to undergo all of this if we do not know that we are providing benefit, especially since the vast majority of them will never get into trouble even if they are not treated? A number of inception cohort studies (long-term followup of an entire population of infected individuals, including my own (Ann Intern Med 1993119:110-5) have indicated that the risk of decompensated cirrhosis or cancer is closer to 10%. Furthermore, epidemiologic data indicate that most infected individuals will never get into trouble. (For example, if there are 4,000,000 carriers in the United States, as well as 10,000 annual deaths [the figures that are widely cited to indicate the impact of these infections], the average time that it would take to get into trouble [latent phase] is 400 years). We also know that not everybody who has an SVR is protected from the subsequent development of end-stage liver disease or hepatocellular carcinoma (e.g., Hofer, Hepatology 200950	Comment noted. The Committee provides guidance on the use of cost-effective technologies in the NHS. The most appropriate treatment for a patient is decided by their clinician, after discussion with their patient and careful consideration of the benefits and risks of available treatment options. No action required.

Role*	Section	Comment	Response
Other (David Geffen School of Medicine, University of California, USA)	4	See above for other comments. The various cost analyses with which I am familiar all suffer from biases that favor the intervention. It is often assumed that non-responders will have the same natural history as would those who had never been treated. Since responders tend to have more favorable characteristics, non-responders likely have a worse long-term course. It cannot be assumed that the life expectancy of hepatitis-C-infected individuals is the same as the normal population, since these people are infected for some reason (typically either a high-risk behavior or a blood transfusion given for some underlying disease such as arteriosclerosis). Some models assume that hepatitis C can only progress in a more severe direction, discounting the possibility of spontaneous recovery or at least the cessation of further inflammation and fibrosis. The natural history of hepatitis C is often derived from studies from tertiary referral centers. Studies of large inception cohorts, as well as epidemiologic considerations discussed above, suggest that the natural history will be less severe.	Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical expert opinions, the Assessment Group's economic analysis and the manufacturer's submissions. It also carefully considered the comments received from consultees and commentators in the response to the Assessment Report. No action required.
Other (David Geffen School of Medicine, University of California, USA)	5	The enthusiasm for treating hepatitis C has largely been based on marketing campaigns rather than convincing data for true (clinical) efficacy. Even the statement that the purpose of treatment is to get rid of the virus misses the point that the real purpose of treatment is to prevent end-stage liver disease. These are not the same. Perhaps NHS funding would be better spent mounting a public education campaign explaining the true risks of the disease, namely the low probability of developing liver failure, and the lack of information about any known true benefits from treatment.	Comment noted. The Committee can make a recommendation for the use of a technology only within the technology's marketing authorisation. The safety and efficacy of a technology is assessed by regulatory agencies before the Appraisal Committee determines whether the technology will be a cost-effective use of NHS resources. The Committee considers all the evidence submitted when making its decision on the use of a technology in England and Wales, No action required.
Other (David Geffen School of Medicine, University of California, USA)	6	The data would suggest that consideration should be given to restricting, rather than expanding, treatment programs for hepatitis C.	Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical expert opinions, the Assessment Group's economic analysis and the manufacturer's submissions. It also carefully considered the comments received from consultees and commentators in the response to the Assessment Report.

Role*	Section	Comment	Response
Other (David Geffen School of Medicine, University of California, USA)	8	The endpoints of therapy that are used in hepatitis C treatment trials are surrogate ones that have never been validated. Data that have emerged from the three large long-term treatment trials of patients with severe histologic disease (HALT-C, EPIC3, CO-PILOT) have indicated that the endpoints could improve even though the patients did not, observations that would be incosistent with the surrogates being valid. The focus on sustained viral responses (SVRs) is an incorrect extension of the HIV model. Â (The vast majority of hepatitis-C infected patients will never get into trouble even if not treated and the serum level of virus may be an epiphenomenon if the virus infects hepatocytes by being in the neighborhood). Since there are prognostic factors for SVRs (little fibrosis, recent infection, female gender, normal weight, etc.), it is incorrect to assume that a 50% SVR rate translates into a 50% reduction in future morbidity. (Many of these factors identify people less likely to get into trouble and disease progression may largely be confined to those who do not respond.) There is insufficiant evidence to recommend treatment based on improvements in these surrogate markers.	Comment noted. The reliability of the available evidence is considered by the Committee when it is formulating its recommendations. No action required.