National Institute for Health and Clinical Excellence

Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C (Part-review of TA75 and TA106)

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	Department of Health	In our view, the background information appears to be generally accurate. The background information refers to data from 2005 about laboratory diagnoses of hepatitis C, reported to the Health Protection Agency (HPA). You may wish to be aware that up to date data (up to and including 2007) is available in the HPA's latest annual report on hepatitis C:, Please see: http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1228810569993?p=1158945066450 For information: the HPA 2007 report indicated that the reporting of laboratory diagnoses was incomplete, perhaps by around 60 per cent; the HPA has estimated that in 2003 there were around 142,000 individuals, aged 15 to 59 years, with chronic hepatitis C infection (95 per cent Credibility Interval (CrI): 90,000-231,000), representing a prevalence in this age group of 0.44 per cent (95 per cent CrI: 0.29, 0.72). The background could, in our opinion, be more explicit about the various routes of transmissions, and could include some indication of treatment success rates by hepatitis C virus genotype.	Comment noted. The background section has been updated.
	Hepatitis C Trust	On page 1 the sentence *In England and Wales, the most prevalent genotypes are 3a (37%), 1a (32%) and 1b (15%)* is no longer correct. According to the latest HPS report Hepatitis C in the UK 2008 the figures are 3a (39%), 1a (22%), 1b not given. However, of more importance is the relative size of the easier to treat genotypes 2 and 3. I would therefore suggest deleting the above sentence altogether and adding to the following sentence so it reads *Genotype is a key predictor of the effectiveness of anti-viral treatment and patients with genotypes 2 and 3, comprising more than half of those infected in England and Wales, generally respond better to treatment than those with genotypes 1, 4, 5 and 6*.	Comment noted. The background section has been updated.

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	Royal College of Nursing	Appears accurate and complete.	Comment noted.
	Schering-Plough	The background information is adequate.	Comment noted.
The technology/ intervention	Department of Health	As far as we are aware, the description is accurate.	Comment noted.
	Royal College of Nursing	Description is accurate.	Comment noted.
	Schering-Plough	The description of the technology is accurate.	Comment noted.
Licensing Issues (only for manufacturers to complete)	Roche Products	1. The extension to Pegasys' licence regarding the retreatment in patients who previously did not respond to interferon (pegylated or non-pegylated) is referring to treatment of both patients that achieved an early virological response but then did not achieve an end of treatment (EOT) sustained virological response (relapsers) and treatment for patients that were treated but did not achieve a virological response (non-responders). 2. The option to shorten treatment duration does only apply to patients with genotype 2 and 3 with low viral load (LVL) at the start of the treatment and rapid virological response (RVR). 3. The updated posology section in Pegasys' SmPC is not a licence extension.	Comment noted. License extension section has been amended to reflect comments.
	Schering-Plough	We anticipate that a paediatric treatment license for our combination therapy pegylated interferon α-2b (PEG-IFN α-2b) plus ribavirin (RBN) may be granted in Europe by the time this appraisal is completed. While exact dates are not known, we would request that paediatric treatment be considered in the current MTA, or in a separate technology appraisal.	Comment noted. Separate appraisal of the paediatric indication is appropriate. The Institute will consider how to take this forward.
Population	Department of Health	We agree that the population appears to be defined appropriately. As far as we are aware, there are no groups to be considered separately, other than the groups that are already mentioned separately in existing technology appraisals.	Comment noted.

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	Royal College of Nursing	It would appear that there are gaps in service provision and the RCN would hope that increased awareness would help with this.	Comment noted.
	Schering-Plough	Please see our comments above regarding paediatric populations. We would request that the scope contain treatment in the paediatric population aged under 18 years. <u>Subgroups by Genotype</u> In treatment of pegylated interferon-based treatment of hepatitis C, treatment pathways as well as outcomes depend on the infected patient's hepatitis C virus (HCV) genotype. Economic analyses carried out by NICE should reflect this by providing separate cost-effectiveness estimates for patients with genotype 1, genotypes 2 and 3, and genotype 4. To accurately reflect differences in treatment pathways and outcomes, patients with genotype 1 should also be divided into those with "high viral load" and "low viral load" as baseline. Please refer to the Schering-Plough and Roche Summaries of Product Characteristics for more detailed definitions of these two categories of genotype 1.	Comment noted. The extent to which clinical effectiveness and cost effectiveness varies according to presence of factors associated with a sustained virological response (for example genotype and baseline viral load) will be estimated for subgroups of patients in whom these factors are present, where data are available.

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	Southampton Health Technology Assessments Centre	The draft scope says “patients with chronic hepatitis C infection” (we assume this includes those with mild, moderate and severe disease) and also mentions patient sub-groups to be “considered” (i.e. those who have been previously treated, etc). Please can you clarify whether the appraisal is to be restricted to just these sub-groups. We are assuming that the sub-groups mentioned are not mutually exclusive. So, for example, people meeting the criteria for receiving shortened courses of pegylated interferon and ribavirin in combination might be treatment naïve, or may have been previously treated. Clarification would be helpful. For the sub-group ‘people who meet the criteria for receiving shortened courses of peginterferon alfa and ribavirin in combination’ – this might need to be specified more clearly as currently it is vague. Do you mean criteria with respect to the changes in the licensed indications mentioned on pages 2/3 of the draft scope?	Comment noted. People with all levels of HCV disease severity will be included. This appraisal is a part-review of TA75 and TA106, and will be restricted to patient subgroups which are affected by the licence extensions for the peginterferons. The subgroups are not mutually exclusive. Patient subgroups which are eligible for shortened treatment courses are determined in line with criteria specified in the SPC for each intervention, e.g. patients with HCV due to genotypes 2 or 3. The scope has been amended to avoid further confusion.
	Department of Health	We feel that it would be helpful to clarify what treatment without any form of interferon therapy would comprise. For example, does “treatment” (in this context) include monitoring of viral load?	Comment noted. For people who have been previously treated with peginterferon alfa and ribavirin in combination, the comparator will be best supportive care, in line with current clinical practice.
	Royal College of Nursing	Yes	Comment noted.
	Schering-Plough	The comparators reflect those used in key trials by Schering-Plough. However, an indirect comparison analysis may be possible and should be considered by the Assessment Group if the data allow.	Comment noted.

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	Southampton Health Technology Assessments Centre	The comparators listed in the scope may not necessarily reflect those used in the clinical trials. For example, one of the trials included in the assessment report for NICE TA 106 which evaluated pegylated interferon and ribavirin in patients co-infected with HIV/HCV used non-pegylated interferon alfa and ribavirin as its comparator. It is unlikely that there will be many trials that compare pegylated interferon alfa and ribavirin against no active treatment.	Comment noted. For people who have been previously treated with peginterferon alfa and ribavirin in combination, the comparator will be best supportive care, in line with current clinical practice. Where clinical trials do not compare the intervention of interest to current standard of care, indirect comparison analyses can be conducted.
Outcomes	Department of Health	We agree with this statement.	Comment noted.
	Royal College of Nursing	Yes	Comment noted.
	Schering-Plough	The outcomes list is adequate.	Comment noted.
	Southampton Health Technology Assessments Centre	These are consistent with those included in the previous appraisals.	Comment noted.
Economic analysis	Department of Health	We have no comments to make.	Comment noted.
	Royal College of Nursing	As these drugs are extremely expensive, the RCN would welcome comments from the manufacturers regarding this.	Comment noted.
	Schering-Plough	We would comment that a lifetime timeframe is typically used in this field, as mortality plays a significant part in the balance of outcomes.	Comment noted.
	Southampton Health Technology Assessments Centre	This is consistent with the scope of the previous NICE appraisals of hepatitis C treatment	Comment noted.

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Other considerations	Department of Health	We have no comments to make.	Comment noted.
	Roche Products	Roche believe that it is appropriate to limit the appraisal to the new indications only.	Comment noted.
	Southampton Health Technology Assessments Centre	No comments other than the point made above that there are likely to be few trials of no active treatment as a comparator, and also the need for clarification as to whether the scope is restricted to the sub-groups mentioned or whether all patients with hepatitis C are eligible (i.e. a full review of the previous guidance)	Comment noted. This appraisal is a part-review of TA75 and TA106, and will be restricted to patient subgroups which are affected by the licence extensions for the peginterferons.
Additional comments on the draft scope.	Department of Health	We have no other comments, except that the review of the guidance is welcome, in view of the extensions to the drug licences.	Comment noted.
	Hepatitis C Trust	We do feel there is a need for guidance for the treatment of children. However, we do not feel there is sufficient evidence as yet. We would therefore like to ask NICE to call for trials to produce the required evidence. In particular, we would like any trials to consider teenagers and pre-teenagers as separate sub-groups as, from anecdotal evidence, we believe there may be significant differences in tolerability between the two groups	Comment noted. An appraisal of the paediatric indication is appropriate. The Institute will consider how to take this forward.
	Roche Products	Roche believe that paediatric treatment of chronic hepatitis C should be considered in a separate technology appraisal.	Comment noted. Separate appraisal of the paediatric indication is appropriate. The Institute will consider how to take this forward.

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	Royal College of Nursing	Question 1: A review of the previous guidance is timely and appropriate. One assumes that the new indications are based on the changes to drug licences, and therefore the assumption is that such changes have been approved as appropriate to clinical practice? Question 2: The preference would be to review 'watchful waiting'. There is some lack of detail in the document so it may be that we just do not have all the information at hand however, it is unclear if cost and clinical effectiveness of this approach has been evaluated. We are a bit concerned about how patient decisions can be evaluated and audited in order to evaluate such a decision. The draft scope (page 2) states that for the majority of people with hepatitis C, regardless of severity, the standard treatment is combination therapy. Why then is 'watchful waiting' instigated, we are unsure of the rationale for this. Question 4: It seems appropriate to have a specific appraisal for children.	Comment noted. The review is being conducted to consider the clinical and cost-effectiveness of licence extensions to the peginterferons which have been granted after the publication of previous guidance (TA75 and TA106). NICE guidance TA106 currently recommends that the decision on whether a person with mild chronic hepatitis C should be treated immediately or should wait until the disease has reached a moderate stage ('watchful waiting') should be made by the person after fully informed consultation with the responsible clinician about treatment side effects. Separate appraisal of the paediatric indication is appropriate. The Institute will consider how to take this forward.

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	Schering-Plough	By limiting itself to only consider new indications, the new guidance will omit new evidence collected for existing indications since the publication of TA75 and TA106. The most important evidence collected by Schering-Plough comes from the IDEAL trial (Study ID P03471, completed 2008) which showed that patients with genotype 1 HCV respond differently to treatment depending on whether they receive PEG-IFN α-2a plus RBN or PEG-IFN α-2b plus RBN. Namely, while the sustained virological response rates were similar for both therapies, patients receiving PEG-IFN α-2b plus RBN demonstrated better predictability at week 12 and were less likely to relapse after an end-of-treatment response than patients receiving PEG-IFN α-2a plus RBN. Were the existing NICE guidance on pegylated interferons overhauled, we would not expect that data from the IDEAL trial would materially alter existing NICE guidance, i.e. it would not lead to the rejection of drugs previously recommended. However, the data could lead to differential budget impact estimates for PEG-IFN α-2a & RBN and PEG-IFN α-2b & RBN and consequently different cost-effectiveness estimates.	Comment noted. Since the IDEAL trial is not expected to materially alter existing NICE guidance, the focus of this appraisal will be the licence extensions to the peginterferons.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

British Liver Nurses' Forum
UK Haemophilia Alliance
Welsh Assembly Group