NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Peginterferon alfa and ribavirin for treating chronic hepatitis C in children and young people (ID373)

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
Merck Sharp & Dohme	**NICE Recommendation**	**Comments**	
	1 Appraisal Committee's preliminary recommendations		
	1.1 Peginterferon alfa in combination with ribavirin is recommended, within its marketing authorisation, as an option for treating chronic hepatitis C in children and young people.	MSD agree with the preliminary recommendations made by the Appraisal Committee.	Comment noted. No action required.
	3 The Technologies		
	3.2 Summary of the marketing authorisations for ribavirin	For the purpose of clarity, MSD would recommend the summary of the marketing authorisations for ribavirin are reported as a separate recommendation.	Comment noted. The marketing authorisations of each ribavirin have been described separately in the FAD in section 3.3.
	4 Evidence and Interpretation		
	4.1.3 A single-arm clinical trial evaluating peginterferon alfa-2b and ribavirin (Wirth et al. 2008, n=107) included children and young people aged 3–17 years.	The year for the reference is incorrect. It should be Wirth et al. 2010.	Comment noted. The correction has been incorporated into the FAD.
	4.1.8 The Pawlowska et al. study presented sustained virological response by genotype subgroup, but the numerators in each subgroup did not add up correctly to the total number of treatment-naive and previously treated patients in the trial, and the numbers in these subgroups were small.	Please note that the numerators in each subgroup did not add up to the total number of study participants because patients with genotype 3 HCV were excluded (as stated).	Comment noted. Section 4.1.8 of the FAD has been updated to reflect that the patients with genotype 3 HCV were excluded from the subgroups.
	4.1.11 The proportion of children and young people whose hepatitis C relapsed was reported by Schwarz et al. (17%) and in 4 peginterferon alfa-2b studies	For the purpose of consistency, please include the proportion of relapse reported by Ghaffar et al. (14.28%) in this paragraph.	Comment noted. The Assessment Group

Consultee	Comment		Response
	(8% in Al Ali et al.; 17% in Pawlowska et al.; 8% in Wirth et al. [12% for genotype 1]; 3% in Jara et al.). Two of the peginterferon alfa-2b studies (Al Ali et al.; Ghaffar et al.) reported data that the Assessment Group inferred to be relapse of hepatitis C.		did not include the Ghaffar et al. study as having reported relapse. The last sentence in 4.1.11 should have referred to Al Ali et al. and Jara et al and this has been corrected in the FAD.
	4.2.11 …MSD used transition probabilities from previous technology appraisals on the treatment of chronic hepatitis C in adults; it used the same transition probabilities across all genotypes, because no child-specific transition probabilities were available….	MSD would like to reference section 6.7.1 in our submission dossier. In this section, details are provided of a systematic review undertaken on the natural history of HCV in children and young people. As a result of the review child-specific transition probabilities were obtained for Mild HCV to Moderate HCV and Moderate HCV to Compensated Cirrhosis (CC). As it is uncommon for children to progress to more severe stages of HCV before adulthood, the use of child-specific transition probabilities between the Mild, Moderate and CC heath states and the use of adult transition probabilities in the more severe HCV health states, is an appropriate representation of disease progression for this patient population. Please refer to Table 23 and Table 24 for included transition probabilities.	Comment noted. This section of the FAD has been amended accordingly.
	4.2.14 MSD used health-state costs presented in previous appraisals of adults because it did not identify any published evidence on costs associated with chronic hepatitis C in children and young people. The costs associated with having a sustained virological response for those starting with mild to moderate hepatitis C were applied for 5 years in the model, while the costs associated with having a sustained virological response	MSD would like to highlight this statement is correct, however it does not mention that the resource use and costs for monitoring while on treatment including follow-up visits after the completion of treatment, and follow-up for those with SVR were child-specific. Please see “Treatment-related costs: treatment initiation, on-treatment and post-treatment monitoring” (pg 62) within section 6.7.4.1 of MSD’s submission dossier for further explanation.	Comment noted. Section 4.2.14 has been amended to reflect that child-specific costs for monitoring were included in the MSD model.

Consultee	Comment		Response
	for those starting with cirrhosis were applied over the person's lifetime. The costs associated with each health state were inflated to 2010–11 values using the Hospital and Community Health Services Pay and Price Index used in the economic model.		
	4.2.20 …Another difference between the manufacturers' models was that Roche assumed that some patients have a spontaneous sustained virological response (that is, without treatment), whereas MSD did not….	MSD believe the following is a more accurate statement: *"Another difference between the manufacturers' models was that Roche assumed that some patients have a spontaneous sustained virological response (that is, without treatment) in their base-case, whereas MSD did not include it in their base-case but instead tested this assumption in sensitivity analyses."* Please refer to section 6.11.1 of the MSD submission dossier for explanation of this sensitivity analysis.	Comment noted. The fact that MSD conducted a sensitivity analysis which included the impact of assuming a spontaneous sustained virological response in untreated children has now been included in the FAD.
	4.2.28 …The Assessment Group commented that the deterministic sensitivity analysis for peginterferon alfa-2b compared with peginterferon alfa-2a should be treated with caution because of uncertainty around the relative treatment effect. In most cases, peginterferon alfa-2b was dominated by peginterferon alfa-2a for all changes to the model parameters except for changes to the value reflecting the proportion of people who have a sustained virological response (peginterferon alfa-2a - 51%; or peginterferon alfa-2b - 65%) and the starting age of the cohort (age 5 years).	MSD believe that given the first comment in the corresponding recommendation, the reporting of the results following this statement should be excluded, or if it should remain as a recommendation the results should be reported by genotype as this is more relevant for clinical practice given that genotype is a determining factor for treatment options.	Section 4.2.28 of the FAD is not a recommendation, but rather a reflection of the analyses and comments made by the Assessment Group, which informed the discussion and conclusions made by the Committee. The section has been reworded to provide further clarity.

Consultee	Comment		Response
	4.3.2 The Committee heard from the clinical specialists that the decision to treat children, instead of delaying treatment until a child is symptomatic ('watchful waiting') or reaches adulthood, depends on the age of the child and how the virus is contracted and therefore how likely a spontaneous sustained virological response is without treatment.	MSD would like to highlight that both peginterferon alfa-2a and alfa-2b are only licensed for "chronic hepatitis C", and would therefore they not be prescribed to a child in the acute phase (first 6 months). Once a child has reached the chronic phase a spontaneous viral clearance is less likely that when in the acute phase. Most children in the UK contract HCV via vertical transmission, therefore by the time they are 3 years old, they have had the virus for several years and therefore the probability of spontaneous viral clearance is relatively small compared to those is the acute phase. MSD is unsure whether the distinction was clearly made to the committee of the likelihood of spontaneous viral clearance in the acute phase compared to the chronic phase.	Section 4.3.2 of the FAD has been amended to distinguish between the likelihood of achieving a spontaneous sustained virological response in the acute and chronic phases of hepatitis C infection. It should be noted that the Committee concluded that addressing the impact on the ICERs of achieving a spontaneous sustained virological response would not greatly affect the conclusions about the cost effectiveness of peginterferon alfa plus ribavirin in this appraisal.
	4.3.16 …The Committee considered it appropriate that Roche assumed that a spontaneous 'cure' could occur in a small number of patients in its base case, but noted that this assumption was omitted from the base case analyses of MSD and the Assessment Group, although the Assessment Group did consider the impact of assuming a spontaneous sustained virological response in a sensitivity analysis….	Please note that MSD also considered spontaneous virological clearance in sensitivity analyses. Please refer to section 6.11.1 of the MSD submission dossier for explanation of this sensitivity analysis.	The fact that MSD considered the impact on the ICER of achieving a spontaneous sustained virological response without treatment in a sensitivity analysis has been made clear in section 4.3.16 of the FAD.
	4.3.16 …The Committee heard from the clinical specialists that a spontaneous sustained virological response would probably only occur before the age of 4 years…	MSD would like to refer NICE to our comment above corresponding to section 4.3.2.	This comment has been reflected in the changes made to section 4.3.16 of the FAD.

Consultee	Comment		Response
			This comment has been reflected in the changes made to section 4.3.17 of the FAD.
	4.3.17 The Committee was aware that the Roche model did not take into account costs associated with hepatitis C after treatment. It heard from the clinical specialists that this was a realistic assumption and that paediatric patients, once successfully treated, were not referred to adult hepatology clinics.	MSD agrees with the corresponding recommendation, however if a paediatric patient had any signs if liver damage (i.e. cirrhosis) they would continue to be seen by a clinician for possibly the rest of their lives even if successfully treated, according to our clinical expert opinion. The MSD model assumed paediatric patients successfully treated with mild or moderate disease were followed-up for 5 years post treatment and those with compensated cirrhosis required follow-up for the rest of their life.	
	Summary of Appraisal Committee's key conclusions		Comment noted. 'Peginterferon alfa' is used consistently throughout the FAD.
	Proposed benefits of the technology (4.3.7) Treatment with peginterferon could provide a sustained virological response that could potentially last for the lifetime of the child or young person, effectively providing a cure.	MSD would kindly ask that 'peginterferon' is reported as 'peginterferon alfa' to ensure consistency throughout the report.	The summary table has been amended to reflect that MSD did conduct a sensitivity analysis of the impact on the ICER of assuming a spontaneous sustained virological response can occur in untreated children.
	Uncertainties around and plausibility of assumptions and inputs in the economic model (4.3.16) Spontaneous sustained virological response without treatment was not included in the model and should be included in future submissions.	Recommendation 4.3.16 states that spontaneous sustained virological response without treatment should be included in sensitivity analyses, which MSD is in agreement with. This summary should reflect this recommendation by specifically stating it is included in sensitivity analyses.	
Royal College of Paediatrics and Children's Health	Page 42 1.1	I agree with the key conclusion of 'Peginterferon alfa-2a plus ribavirin and peginterferon alfa-2b plus ribavirin are recommended as treatment options, within their licensed indications, for children and young people with chronic hepatitis C'.	Comments noted. No action required.

Consultee	Comment		Response
	Page 44 4.3.4	I am however, slightly concerned that the systematic reviews conducted by the manufacturers and the Assessment Group identified few relevant studies in children and young people and these studies were small and of generally poor quality although this finding is not unexpected.	
	Page 44 4.3.5	I am reassured that the average age of entry into the trials reflected the average age of children and young people currently treated in the UK and therefore was satisfied that the trial results were largely generalisable to the UK population.	
Royal College of Nursing	The Royal College of Nursing (RCN) was invited to review the Appraisal Consultation Document (ACD) for **Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C in children and young people [ID373]** Nurses caring for people with hepatitis C reviewed the documents on behalf of the RCN. **Appraisal Consultation Document – RCN Response** The Royal College of Nursing welcomes the opportunity to review this document. The RCN's response to the questions on which comments were requested is set out below: i) **Has the relevant evidence been taken into account?** The relevant evidence available has been taken into account appropriately and reasonable interpretations made relating to the treatment of chronic hepatitis c in children and young people. The recommendations are a sound and suitable base for guidance but there will be further work required by local Hepatology networks and individual clinicians as to where patients are to be treated (ie should this be limited to specialist tertiary liver centres) and further local guidelines for age of commencement in relation to level of fibrosis, issues around pre and post puberty and considerations in patient choice. ii) **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The RCN has no comments to submit. iii) **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**		Comments noted.

Consultee	Comment	Response
	"Peginterferon alfa-2a (Pegasys, Roche Products)The recommended treatment duration is 24 weeks (genotypes 2 or 3) or 48 weeks (all other genotypes) depending on baseline viral load and whether or not a child has a virological response (defined as a 100-fold decrease in, or undetectable levels of, serum HCV RNA) at weeks **4 and 24".** Is this stopping rule correct? Should this read 12 and 24? iv) **Could the preliminary recommendations have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology or have any adverse impact on people with a particular disability or disabilities?** The RCN has no comments to submit.	The recommended treatment duration for peginterferon alfa-2a is 24 weeks for genotypes 2 and 3 HCV. There is no stopping rule specified in the marketing authorisation for treating children with chronic hepatitis C. This has been reflected in changes to section 3.1 of the FAD.
Roche	Thank you for the opportunity to provide comments on the ACD for peginterferon alfa and ribavirin. In this instance, we have no comments on the ACD. Please let us know if you require anything further from us.	n/a
Department of Health	Thank you for the opportunity to comment on the appraisal consultation document (ACD) for the above multiple technology appraisal. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	n/a

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Healthcare Improvement Scotland	1. Do you consider that all the relevant evidence has been taken into account? If not, what evidence do you consider has been omitted, and what are the implications of this omission on the results? *The published evidence has all been considered. However it has to be recognised that there are few high quality trials, and most of the evidence arises from observational studies.* *2.* Do you consider that the analysis of clinical and cost effectiveness has used an appropriate comparator which reflects Scottish practice?	Comments noted.

Nominating organisation	Comment	Response
	In general yes, but the age of 11 is probably not the most appropriate to base the "average". Most clinicians treating children would choose, if treating, to treat at an earlier age, and few would choose to treat those approaching or having entered adolescence. Some of the reasons are cited in the text, such as effect of growth, but also, psychiatric problems, and issues with adherence are much more common in the adolescent population. Clearly the average age, and therefore weight (or surface area) affects the dose and therefore the economic analysis	The Committee was satisfied that the trial results were largely generalisable to the UK population. The Committee also noted that the economic results were largely robust to changes in variables within the model, including age entering the model.
	3. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence? If not, in which areas do you consider that the summaries are not reasonable interpretations?	
	For favourable genotypes yes. There was no assessment of the effect on quality of life of those who have started, but failed treatment. This is a significant issue in those with less favourable genotypes (1,4,5). It cannot be assumed that this is unaffected by the intervention, as this group may have suffered adverse events (such as growth arrest) without any long term benefit. The treatment itself, particularly as it involves weekly injections is traumatic for some children, and may result in needle phobia which affects their ongoing care. If cured, their subsequent exposure to needles is minimal, but not if they do not achieve SVR. The watch and wait comparator also assumes no treatment at any time in the future. As new technologies are on the doorstep, some which may allow treatment without interferon (ie without injection) clinicians may choose to watch and wait until	The Committee has noted that new technologies are becoming available and are currently licenced for adults. These technologies would have to be licensed for treatment in the UK in the corresponding age group before they can be considered as a comparator technology in any appraisal.
	4. Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? If not, why do you consider that the recommendations are not sound?	
	Yes, in that the recommendation is that the treatment should be available to clinicians – implying that patients will be treated based on the clinician's clinical judgement of the individual case. This is in contrast to a guideline or recommendation that patients should be treated.	Peginterferon alfa-2a and peginterferon alfa-2b are recommended as an option for treating chronic hepatitis C in children and young people. The decision about whether and when to treat should be made by parents or carers together with the child's or young person's clinician.
	5. Are the patient pathways and treatment options described in the assessment applicable to NHSScotland? If not, how do they differ in Scotland?	

Nominating organisation	Comment	Response
	In the text there is a reference to treatment currently only being available in specialist paediatric hepatology centres in the UK. This is factually incorrect, as treatment is already available in Scotland, in specialist centres with experience in the management of viral hepatitis. Treating clinicians may be from a paediatric GI/hepatology, or from a paediatric infectious diseases background, similar to the service provision for adults in Scotland. It is, however, essential that those treating have appropriate expertise. Networking will therefore be essential in order to ensure that there is equality of access to treatment throughout Scotland. Given the evolution of networks in other related areas, such as that for HIV/Primary Immunodeficiency, which involve some of the same clinicians as those treating viral hepatitis, Scotland may well be better placed than other UK countries to deliver this technology.	Comment noted. The FAD has been amended to reflect that treatment is only currently available in specialist paediatric hepatology centres in England and Wales.
	6. Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? If so, please describe what these changes would be. *Pathways would not need to change but will need further development to ensure that all eligible children are assessed and treated if appropriate.*	Comments noted.
	7. Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? If yes, please explain why this is the case. *No, taking into consideration the comments above*	
	8. Please add any other information which you think would be useful to NICE or helpful in guiding the Scottish response to this assessment *As mentioned above, the importance of being aware of new technologies, and the importance of inclusion of children in clinical trials of these technologies in order to inform future evidence cannot be over-emphasised.*	

Comments received from commentators

No comments received from commentators.

Comments received from members of the public

No comments received from members of the public.