The clinical and cost-effectiveness of peginterferon alfa and ribavirin for the treatment of chronic hepatitis C in children and young people

SHTAC Responses to consultees comments on Assessment Report 11th June 2013

Section	MSD comment	SHTAC response
MSD		
Effectiveness of peginterferon alfa	Although MSD acknowledge that the clinical trials providing evidence for the efficacy of peginterferon alfa-2a and -2b for children and young people with HCV were relatively small and generally of poor quality, MSD would highlight that the evidence from all the included clinical studies establishes that these treatments are effective in this population. In addition, several of the studies established that efficacy in children and young people is likely to be similar to that seen in adults.[1,2,3,4,5,6] It is also clear that after early childhood HCV infection will not spontaneously resolve,[7,8] therefore, the sustained virological response (SVR) for best supportive care (BSC) would be 0. MSD would conclude that efficacy is demonstrated by the studies, despite the fact that they are small and uncontrolled.	No action. The clinical evidence largely comes from studies with small patient numbers and poor methodological quality and therefore efficacy is not conclusively demonstrated, hence the current wording.
Control group of BSC for the paediatric studies	The assessment report states the lack of head-to-head studies of peginterferon alfa vs. BSC to be a limitation of the analyses. However, MSD would suggest that a control group of BSC for the paediatric studies would provide little benefit. HCV is a slowly-progressing disease so an untreated control group followed for 5 years would provide very little insight into the natural history of the disease given the size and scope of the paediatric studies.	This comment is noted, however, no action is required as this remains a limitation of the analysis.
Suggested research priorities	The report suggests (section: "suggested research priorities") that a study should be performed to compare peginterferon alfa-2a and alfa-2b. It is unlikely that given the size and scope of paediatric trials that this type of study could be adequately powered. The major reference for comparability of the two peginterferon alfa products is the IDEAL study[9] in approximately 3000 adult patients, where no difference in efficacy was observed. MSD would expect that these findings would not differ in a paediatric population.	No action. This suggestion stemmed from the lack of head-to-head evidence available in this patient group and acknowledges such studies are unlikely.
Conclusions based on the cost-effectiveness	Overall, MSD have a positive view of the cost-effectiveness analysis performed by the Assessment Group. MSD has the view that the	We agree with this and will remove the statement: "and peginterferon α-2a is

analysis	only conclusions that can be drawn from the cost-effectiveness analysis are equivalent to those from the cost-effectiveness analysis submitted by MSD: both peginterferon alfa-2a and peginterferon alfa-2b are cost-effective treatments for children and adolescents between the ages of 5 to 17 years with HCV, and peginterferon alfa-2b is cost-effective for the treatment of children aged between 3 and 4 years with HCV. MSD believe that less emphasis should be given to the cost-effectiveness of peginterferon alfa-2a versus peginterferon alfa-2b given the poor quality evidence that is available to conduct a comparison between the two treatments, as reported on page 66 of the report. MSD felt the main body of the report did emphasise that caution should be used when interpreting the economic evaluation as "there was no means to assess the similarity of the included studies", as reported on page 94; however this view was not reflected in the abstract which concluded that peginterferon alfa-2a was cost-effective compared to peginterferon alfa-2b. The conclusion in the abstract and Table 46 gives the impression that peginterferon alfa-2a dominated alfa-2b in all scenarios, which is not the case. For example, peginterferon alfa-2b is cost-effective compared with peginterferon alfa-2a in more than 30% of the scenarios according to Figure 10.	more cost-effective than peginterferon α-2b" from the abstract. For Table 46, this is a summary of the PSA results, in which PEG α-2b is dominated by Peg α-2a. We have acknowledged the limitations of the evidence base and urged caution when comparing Peg α-2a and Peg α-2b. For clarity another caveat for Table 46 will be added to state: As stated above (section 5.4.2), there is uncertainty of the reliability of the relative SVR effect size between peginterferon α-2a and α-2b.
3-4 year age-group analysis	In the cost-effectiveness section, MSD believe that the Assessment Group failed to recognise the remit according to the scope of this MTA by not reporting the cost-effectiveness of peginterferon alfa-2b for the treatment of children with HCV between the ages of 3 to 4. An additional cost-effectiveness analysis should have been conducted for this age group and results reported separately.	We recognise that peginterferon α-2b should be compared to BSC only for 3 and 4 year olds as per the license. However, there is no specific evidence for this age group alone. Our base case analysis used a starting age of 11 years based on the mean age of children in the clinical effectiveness studies, which included children of ages 3 and 4 for peginterferon α-2b. Our sensitivity analyses for different age groups (deterministic sensitivity analyses, Table 40-42) showed that there are no marked differences for

		starting age 5 years. We anticipate results for those aged 3 and 4 years will be of similar magnitude.
Meta-analysis of overall SVR rates used in the cost-effectiveness model	MSD would like to emphasise the bias in the estimates of the overall SVR rates as a result of how they have been calculated in the base case. The overall SVR rates were combined using the weighted average of the SVR rates for genotypes 1/4 and genotypes 2/3 and their associated sample proportions based on clinical trial data for each peginterferon. As the SVR rates for both treatments are significantly higher for the genotype 2/3 patients, any trial with a higher proportion of genotype 2/3 will bias the overall SVR rate for one treatment over the other. This was the case for peginterferon alfa-2a for which the proportion of patients with genotype 2/3 was 23% compared to 18% for peginterferon alfa-2b. This can be corrected for by using an equal distribution of genotype 1/4 and 2/3 for both treatments. This could also improve the robustness of the estimation of the overall SVR rates if the distribution in the clinical trials does not match that in clinical practice. MSD had feedback from a Key Opinion Leader that the actual split was closer to two thirds of genotype 1/4 and one third of genotype 2/3. MSD appreciate that this is the view of only one clinician, but recommend that the proportions are the same across both treatments. MSD believe this is a major source of uncertainty in the comparison of both peginterferons given that the model is driven by the comparative SVR rates for peginterferon alfa-2a and peginterferon alfa-2b. The Assessment Group did run a scenario analysis with equal distribution and the results of the model did show equal QALYs and a slight cost advantage to peginterferon alfa-2a, which MSD believe is a more appropriate estimate for the base case.	The method used in the base case results directly uses the clinical evidence available. We acknowledge in our report the uncertainties around the data. This uncertainty has been explored in sensitivity analyses. In addition, we included a scenario analysis varying the treatment effectiveness of SVR of peginterferon α-2b. These analyses demonstrate the uncertainty in the base case results. We acknowledge in this section the uncertainty about the reliability of the relative SVR effect sizes between peginterferon α-2a and peginterferon α-2b, due to the poor quality of the studies and the lack of head-to-head trials. No action required.
Copegus license	The licence for Copegus does not cover children and young people under the age of 18 years. As NICE does not assess treatments outside of licence Copegus should be excluded from the analyses. As Rebetol is the only brand of ribavirin licensed in the population included in the scope, the cost-effectiveness analysis should be conducted with both peginterferon alfa-2a and peginterferon alfa-2b in	We note that this statement is inconsistent with the approach taken by MSD, where Copegus has been used in the analyses. In addition, Roche (manufacturer of peginterferon α-2a) have also used copegus in their

	combination with Rebetol. The consequence of this would be an increase in the cost of treatment associated with peginterferon alfa-2a.	analyses. At the time of writing the report, Rebetol was already licensed for use in children and young people 3-17 yrs but the Rebetol EPAR specifically states that it is to be used in combination with peginterferon α-2b. Copegus was indicated for use with peginterferon α-2a and was awaiting the paediatric licence. We note that Roche now have the licence for peginterferon α -2a and ribavirin for children ≥5 yrs but we have not been able to establish whether Copegus is similarly licensed as it is no longer listed on the EMA website. For information, we have run a sensitivity analysis using peginterferon α-2a with rebetol. In this analysis the total cost for peginterferon α-2a increases from £19,055 to £19,617. This increase in cost does not change the results significantly and peginterferon α-2a continues to dominate peginterferon α-2b.
Table 32, page 100	A minor point - there is a mistake in the headings in Table 32 on page 100 - the headings for weight and height need to be switched.	We agree. Title headings will be corrected as suggested.
Roche		
	We confirm that peginterferon alpha-2a in combination with ribavirin is now authorized for the treatment of chronic hepatitis C in treatment-naïve children and adolescents 5 years of age and older who are positive for serum HCV-RNA.	Extension of the license was approved by CHMP on 22/3/13. An amendment will be made in the Executive Summary and Section 1.3 (p.24) to reflect this.
Implications for service provision, p.13	We disagree with the comments made in the Implications for service provision section of the Assessment Report. We believe requiring expertise in paediatrics should not be weighted	No action. The report states that shared-care pathways between the specialised

	so heavily against the general expertise in managing hepatitis C. Children should have the option to be treated in centres beyond the 3 specialised paediatric hepatology centres. This would allow children and their mothers to be seen by the same specialists and maintain their continuum of care.	centres and other treatment centres are well-established.
Hepatitis C Trust		
Background – Aetiology, p.16	It states - from contaminated blood products prior to 1991. In fact that refers to contaminated blood. Blood products were heat treated (for HIV) from the mid 1980s (1985 England, 1987 Scotland) and contamination from blood products would therefore only have occurred prior to the mid 1980s.	We agree. Text will be amended in Section 1.1 (p.16) to reflect this.
	The economic assessment excludes any costs for 'onward transmission'. We strongly feel this is a serious and unnecessary omission.	No action. The method used to model hepatitis C is consistent with that developed for adults (Shepherd et al. 2007; Hartwell et al. 2011), which explicitly noted that it did not consider the impact of onward transmission of HCV. This is acknowledged as an assumption on page 91 of the present assessment report.
	The assessment of growth impairment appears only to have looked at the studies that were included in the overall effectiveness assessment. Please look at Effects of pegylated interferon-α-2a monotherapy on growth in Japanese children with chronic hepatitis C Tomoyuki Tsunoda1,*, Ayano Inui1, Manari Kawamoto1, Tsuyoshi Sogo1, Haruki Komatsu2, Tomoo Fujisawa1Article first published online: 24 APR 2013 and PEG-IFN led to loss of weight, height, BMI in children with HCV Jonas MM. Hepatology. 2012;doi:10.1002/hep.25690	No action. AE were reported from studies that met the inclusion criteria. In the study by Tsunoda, children were treated with peginterferon α-2a monotherapy; the study by Jonas includes a mixture of children who had received peginterferon α-2a + RBV and peginterferon α-2a monotherapy with no separate reporting of results. Since monotherapy in this patient group is not permitted in the marketing authorisation, the results from these studies were not included.
	We can see no discussion on whether side effects of treatment may be different	Noted. No action.

	depending on the age of the child. Anecdotally we have noted that psychological side effects may be worse during puberty, when interferon may potentiate other hormonal changes.	
	We are not sure how this can be included but one of the 3 specialist centres suggested a single working mother should do HCV treatment at the same time as her teenage child. We consider this advice to be at best ill-judged, since we would recommend against adult partners doing treatment simultaneous, since we have enough anecdotal evidence to believe this to be hugely problematic.	This comment does not relate to any evidence noted in the assessment report. No action.

MSD references

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[3] Al Ali J, Owayed S, Al-Qabandi W, Husain K, Hasan F. Pegylated interferon alfa-2b plus ribavirin for the treatment of chronic hepatitis C genotype 4 in adolescents. Ann Hepatol. 2010; 9(2): 156-60.
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