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4th June 2013

Dear Jeremy,

RE: **Assessment Report for the NICE MTA of peginterferon and ribavirin for the treatment of children and young people with HCV**

Thank you for providing the opportunity to review and comment on the Assessment Report for this MTA. MSD are appreciative of the amount of work that has been undertaken by the Assessment Group in producing the report.

MSD have now reviewed the Assessment Report and our comments are outlined below. If you have questions or require any additional information, please do not hesitate to contact me.

Yours sincerely,

[redacted]

HTA & EBM Manager
MSD

MSD response to the Assessment Report for the NICE MTA of peginterferon and ribavirin for the treatment of children and young people with HCV

Comments on the Assessment Report

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.
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.
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.
Conclusions based on the cost-effectiveness analysis	Overall, MSD have a positive view of the cost-effectiveness analysis performed by the Assessment Group. MSD has the view that the 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.
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.

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.
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 combination with Rebetol. The consequence of this would be an increase in the cost of treatment associated with peginterferon alfa-2a.
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.

[1] Jara P, Hierro L, de la Vega A, Diaz C, Camarena C, Frauca E, *et al*. Efficacy and safety of peginterferon-α2b and ribavirin combination therapy in children with chronic hepatitis C infection. Pediatr Infect Dis J. 2008; 27(2):142-8.
[2] Schwarz KB, Gonzalez-Peralta RP, Murray KF, Molleston JP, Haber BA, Jonas MM, *et al*. The combination of ribavirin and peginterferon is superior to peginterferon and placebo for children and adolescents with chronic hepatitis C. Gastroenterology. 2011; 140: 450-8.
[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.
[4] Pawłowska M, Pilarczyk, Halota W. Virologic response to treatment with pegylated interferon alfa-2b and ribavirin for chronic hepatitis C in children. Med Sci Monit. 2010; 16(12): 616-21.
[5] Wirth S, Ribes-Koninckx C, Calzado MA, Bortolotti F, Zancan L, Jara P, *et al*. High sustained virologic response rates in children with chronic hepatitis C receiving peginterferon alfa-2b plus ribavirin. J Hepatol. 2010; 52: 501-7.
[6] Sokal EM, Bourgois A, Stéphenne X, Silveira T, Porta G, Gardovska D, *et al*. Peginterferon alfa-2a plus ribavirin for chronic hepatitis c virus infection in children and adolescents. J Hepatol. 2010; 52: 827-31.
[7] Wirth S, Kelly D, Sokal E, Socha P, Mieli-Vergani G, Dhawan A, *et al*. Guidance for clinical trials for children and adolescents with chronic hepatitis C. J Pediatr Gastroenterol Nutr. 2011; 52(2): 233-7.
[8] Bortolotti F, Verucchi G, Cammà C, Cabibbo G, Zancan L, Indolfi G, *et al*. Long-term course of chronic hepatitis C in children: from viral clearance to end-stage liver disease. Gastroenterology. 2008; 134: 1900-7.
[9] McHutchinson JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, *et al*. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med. 2009; 361: 580-93.