MSD response to the appraisal consultation document for peginterferon alfa and ribavirin for treating chronic Hepatitis C in children and young people

Dear NICE

MSD welcome the opportunity to consult on the appraisal consultation document for peginterferon alfa and ribavirin for treating chronic hepatitis C in children and young people.

Overall, MSD agree with the recommendations made by the NICE committee in the appraisal consultation document. Our comments below primarily relate to the correction of factual inaccuracies.

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.
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.
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.
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).

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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 (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.	For the purpose of consistency, please include the proportion of relapse reported by Ghaffar et al. (14.28%) in this paragraph.
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.
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 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.	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.

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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.
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.
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

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	spontaneous viral clearance in the acute phase compared to the chronic phase.
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.
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.
4.3.7 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	
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.
Uncertainties around and plausibility of assumptions and inputs in the	Recommendation 4.3.16 states that spontaneous

economic model (4.3.16) Spontaneous sustained virological response without treatment was not included in the model and should be included in future submissions.	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.