

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

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

1 Guidance

- 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.

2 Clinical need and practice

- 2.1 Hepatitis C is a disease of the liver caused by the hepatitis C virus (HCV). The presence of HCV RNA (ribonucleic acid) in serum indicates infection. There are 2 main phases of infection: acute and chronic. Acute hepatitis C refers to the period immediately after infection, whereas chronic hepatitis C is defined as infection that lasts for more than 6 months. In the UK, there are 2 major routes of HCV transmission: sharing needles in intravenous drug misuse and receiving transfusions of infected blood or blood products. However, children acquire the virus primarily from their mothers at birth. Breast feeding does not appear to increase the risk of HCV transmission.
- 2.2 Six main genetic types of HCV, known as genotypes 1 to 6, with further subtyping (a–j) have been found. In England and Wales genotypes 1 and 3 account for more than 90% of all diagnosed infections. The effectiveness of antiviral treatment depends on the viral genotype; the response is generally better in people infected

with genotypes 2 or 3 than in those infected with genotypes 1, 4, 5 or 6.

- 2.3 Infection with HCV can lead to complications, including hepatic dysfunction, hepatic cirrhosis, hepatocellular carcinoma and death. Progression to severe hepatitis or cirrhosis during childhood is rare (less than 5%) and the mean time to development of cirrhosis in people infected as infants is estimated to be 28 years.
- 2.4 Estimates from the Health Protection Agency in 2011 show that HCV was newly diagnosed in 26 people aged 1 year or younger and 21 people aged 1–14 years in England in 2010. Estimates for chronic infection in children and young people in the UK are not available.
- 2.5 The aim of treatment is to clear the virus from the blood. Sustained virological response, defined as undetectable serum HCV RNA 6 months after the end of treatment, usually indicates resolved infection, although relapse occurs in approximately 5% of people after 5 years.

3 The technologies

- 3.1 Peginterferon alfa-2a (Pegasys, Roche Products) in combination with ribavirin has a UK marketing authorisation for the treatment of children and adolescents 5 years of age and older with chronic hepatitis C, who test positive for serum hepatitis C virus (HCV) ribonucleic acid (RNA) and who have not previously received any treatment. Peginterferon alfa-2a is administered subcutaneously once weekly. The dose depends on body surface area, and it should not be used in children with a body surface area of less than 0.71 m² (for whom there are no data). 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 week 24. Virological response by week 24 is predictive of sustained virological response. If adverse reactions occur, the dose can be reduced.

- 3.2 Peginterferon alfa-2b (ViraferonPeg, Merck Sharp and Dohme [MSD]) in combination with ribavirin has a UK marketing authorisation for the treatment of children aged 3 years and older and adolescents who have chronic hepatitis C without hepatic decompensation, who test positive for serum HCV RNA and who have not previously received any treatment. Dosing of peginterferon alfa-2b for children and adolescents is determined by body surface area and the recommended dose is 60 micrograms/m² per week subcutaneously in combination with ribavirin. The recommended treatment duration is 1 year for children and adolescents with genotype 1 or 4. Treatment should be stopped after 12 weeks if serum HCV RNA decreases less than 100-fold compared with pre-treatment levels or if serum HCV RNA is detectable at week 24. For children and adolescents with genotype 2 or 3, treatment is 24 weeks. If adverse reactions occur, the dose can be reduced.
- 3.3 Ribavirin (manufactured as Copegus by Roche Products), has a marketing authorisation in combination with peginterferon alfa-2a or interferon alfa-2a for treating chronic hepatitis C; the marketing authorisation for Copegus does not include specific recommendations for use in children and young people. Copegus is available as 200-mg or 400-mg tablets. Ribavirin manufactured by MSD (as Rebetol), has a marketing authorisation in combination with peginterferon alfa-2b or interferon alfa-2b for treating chronic hepatitis C in children and young people aged 3 years and older. Rebetol is available as an oral solution and 200-mg hard capsules. The recommended dose of either ribavirin in combination with

peginterferon alfa-2a or -2b is based on body weight; the average daily dose is 15 mg/kg, given in 2 doses. The most common adverse reactions to ribavirin include anaemia, dry cough and rash.

- 3.4 Peginterferon alfa-2a and -2b are contraindicated for treating chronic hepatitis C in children and young people with a history of severe psychiatric conditions. The summaries of product characteristics for peginterferon alfa-2a and -2b mention the following adverse reactions in children and young people: severe psychiatric and central nervous system effects (particularly depression, suicidal ideation and attempted suicide), weight loss and growth inhibition. The summaries of product characteristics state that, when deciding not to defer treatment until adulthood, it is important for clinicians to consider that combination therapy may inhibit growth and that it is uncertain whether this effect is reversible. Therefore the summaries of product characteristics suggest that a child or young person is treated before or after the pubertal growth spurt whenever possible. For full details of adverse reactions and contraindications, see the summaries of product characteristics.
- 3.5 The price of peginterferon alfa-2a is £107.76 for a 135-microgram prefilled syringe or pen and £124.40 for a 180-microgram prefilled syringe or pen (excluding VAT; 'British national formulary' [BNF] edition 65). The price of peginterferon alfa-2b is £1.33 per microgram and it is available in 50-, 80-, 100-, 120- and 150-microgram pens costing £66.46, £106.34, £132.92, £159.51 and £199.38 respectively (BNF edition 65). The Assessment Group calculated that, based on an average age of 11 years, a body weight of 35.5 kg and a body surface area of 1.19 m², a 24-week course of peginterferon alfa-2a plus ribavirin costs approximately £3700 and a 48-week course of treatment costs approximately £7400; a 24-week course of peginterferon alfa-2b plus ribavirin oral

solution costs approximately £4000 and a 48-week course of treatment costs approximately £8100. Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (Section 8) considered evidence from several sources (Section 9).

4.1 Clinical effectiveness

4.1.1 The Assessment Group focused on 5 specific questions to determine the following:

- sustained virological response to treatment
- biochemical response to treatment
- histological response to treatment
- change in quality of life
- adverse reactions to treatment, including effects on growth.

4.1.2 The Assessment Group identified 1 randomised controlled trial and 1 single-arm trial evaluating peginterferon alfa-2a and ribavirin. The randomised controlled trial (Schwarz et al. 2011) was the pivotal regulatory trial for treatment in people aged 5–18 years with chronic hepatitis C. Because the comparator arm was peginterferon monotherapy (that is, without ribavirin), it did not meet the inclusion criteria for the appraisal. Therefore, the Assessment Group used data from the intervention arm (n=55), treating it as an uncontrolled observational study. The single-arm trial (Sokal et al. 2010, n=65) included children and young people aged 6–17 years.

4.1.3 For peginterferon alfa-2b and ribavirin, the Assessment Group identified 5 single-arm studies. A single-arm clinical trial evaluating peginterferon alfa-2b and ribavirin (Wirth et al. 2010, n=107) included children and young people aged 3–17 years. The other 4

studies included populations with narrower age ranges than those specified in the UK marketing authorisation (Al Ali et al. 2010, single-arm trial [n=12, children and young people aged 14–17 years]; Ghaffar et al. 2009 [n=7, children and young people aged 8–16 years]; Jara et al. 2008 [n=30, children and young people aged 3–16 years]; Pawlowska et al. 2010 [n=53, children and young people aged 8–17 years]). The duration of the trials in the Assessment Group’s efficacy review ranged from 24-52 weeks. The Assessment Group found no studies in children or young people co-infected with HIV.

4.1.4 The Assessment Group considered that the quality of the included studies was generally poor because they lacked control groups, except for the study by Schwarz et al., in which the comparison arm was not relevant to this appraisal. The Assessment Group showed that, among other uncertainties, conducting an accurate assessment of the generalisability of the studies was difficult because of substantial variation in the patient inclusion criteria and the countries represented.

4.1.5 The primary outcome of the 7 studies was sustained virological response defined as undetectable serum hepatitis C virus (HCV) ribonucleic acid (RNA) at 24 weeks after the end of treatment (in both peginterferon alfa-2a studies and 4 peginterferon alfa-2b studies) or 12 months after the end of the treatment (Ghaffar et al. study of peginterferon alfa-2b). Concentrations of serum HCV RNA at baseline varied across the 7 included studies. For the 2 peginterferon alfa-2a studies, the sustained virological responses were 53% and 66% in Schwarz et al. and Sokal et al. respectively. For the 5 peginterferon alfa-2b studies, sustained virological response to treatment ranged from 29% to 75%, and proportions in 3 of the studies were comparable to responses seen in the

peginterferon alfa-2a studies (Pawlowska et al., 49% [26/53]; Wirth et al., 65% [70/107]; Jara et al., 50% [15/30]).

- 4.1.6 The 2 studies (Schwarz et al., Sokal et al.) evaluating peginterferon alfa-2a showed that patients with genotype 2 or 3 were more likely to have a sustained virological response than patients with other genotypes (80% to 89% compared with 47% to 57%). In studies evaluating peginterferon alfa-2b, the proportions with a sustained virological response were similar for genotype 1, ranging from 46% to 53%, whereas the proportions achieved for genotype 2 or 3 and genotype 4 varied (50–100% and 0–80% respectively).
- 4.1.7 Both peginterferon alfa-2a studies (Schwarz et al., Sokal et al.) and 1 peginterferon alfa-2b study (Wirth et al.) reported sustained virological responses according to baseline viral load. The results suggest that children and young people with a low baseline viral load (less than 500,000 IU/ml, or 600,000 IU/ml or less) appear to have higher proportions of sustained virological responses (range 70–79%) than those with a higher viral load (more than 500,000 IU/ml, or 600,000 IU/ml or more, range 49–55%). Sokal et al. and Wirth et al. reported that a higher proportion of children and young people with genotype 2 or 3 had a sustained virological response compared with those with genotype 1, 4, 5 or 6, regardless of viral load. Wirth et al. reported that, in people with genotype 1, the proportion having a sustained virological response was higher in those with low baseline viral load than in those with high baseline viral load (72% compared with 29%, $p=0.0006$).
- 4.1.8 The proportions of sustained virological responses in 2 of the studies presented were higher in children and young people who had not been previously treated (55–62%) compared with those who had been previously treated (17–33%). 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 (because study participants with genotype 3 HCV were excluded), and the numbers in these subgroups were small.

- 4.1.9 Three studies reported the proportion of sustained virological responses according to activities of alanine aminotransferase in serum at baseline. In the 2 peginterferon alfa-2a studies (Schwarz et al., Sokal et al.), the proportion of sustained virological responses was higher in those with lower alanine aminotransferase activities at baseline (range 70–80%) compared with those who had higher baseline serum alanine aminotransferase activities (range 41–58%). Sokal et al. showed that, in children and young people with lower baseline alanine aminotransferase activities, sustained virological response did not differ by genotype. However, for children and young people with elevated baseline alanine aminotransferase activities, those with genotype 2 or 3 had a higher proportion of sustained virological responses than those with other genotypes. In the peginterferon alfa-2b study (Wirth et al.), sustained virological response was similar in children and young people with lower and elevated alanine aminotransferase activities at baseline (67% and 64% respectively).
- 4.1.10 Both the peginterferon alfa-2a studies reported sustained virological response according to baseline liver histology. Of children and young people without hepatic fibrosis at baseline, 43% (Schwarz et al. study) and 76% (Sokal et al. study) had a sustained virological response, although the Assessment Group noted the limited numbers in the Schwarz et al. subgroup (n=7). The proportion of children and young people with some degree of fibrosis having a sustained virological response in the 2 studies was 53% and 60% (Schwarz et al. and Sokal et al. respectively).

- 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.; Jara et al.) did not specifically define relapse, but reported data that the Assessment Group inferred to be relapse of hepatitis C.
- 4.1.12 Problems with growth and weight are listed as adverse reactions to treatment in the summary of product characteristics. One study of peginterferon alfa-2a (Sokal et al.) and 3 studies of peginterferon alfa-2b (Pawlowska et al., Wirth et al., Jara et al.) reported changes in height and weight during treatment. Sokal et al. reported that, at baseline and follow-up for height and weight, little influence on growth was seen. Pawlowska et al. reported that treatment with peginterferon alfa-2b and ribavirin had no influence on height at 24 weeks after treatment or 2 years after follow-up. In the remaining 2 peginterferon alfa-2b studies, growth rates decreased during treatment but subsequently recovered. Jara et al. observed that growth during the 48-week treatment period was reduced in 85% of children and young people (22/26) by 1.6 cm compared with the growth velocity fiftieth percentile for age and sex. Growth velocity was described as normal in the 6-month period after the end of treatment; however, patients did not regain their height percentile. Wirth et al. observed that 70% (75/107) of children and young people had an inhibited growth velocity to less than the third percentile for age and sex during treatment. Mean growth velocity was 2.47 cm per year during treatment and 5.73 cm per year in the follow-up period. The decrease in mean height percentile during treatment was greater in children and young people whose treatment duration was longer than in those whose treatment duration was shorter.

- 4.1.13 The 3 studies of peginterferon alfa-2b each reported that patients lost weight during treatment. Jara et al. observed that 67% (20/30) of children and young people lost weight, with 23% (7/30) losing more than 5% of their baseline weight. Weight gain occurred when treatment stopped. Pawlowska et al. observed that 43% (23/53) of patients lost more than 10% of their baseline weight. Wirth et al. reported that 19% (20/107) of children and young people lost weight, with a mean loss in the weight percentile of -15.5 during treatment and a mean gain of 12.3 during follow-up.
- 4.1.14 The Schwarz et al. trial reported changes in quality of life after treatment with peginterferon alfa-2a, assessed using the Child Health Questionnaire – Parent Form 50, and in child and adolescent behavioural and emotional functioning (using the Child Behaviour Checklist), depression (using the Children’s Depression Inventory) and cognitive functioning (using the Behaviour Rating Inventory of Executive Function). The Child Health Questionnaire, Child Behaviour Checklist and Behaviour Rating Inventory of Executive Function instruments were all completed by the child’s parent or guardian, whereas the child completed the Children’s Depression Inventory. Most children and young people (86–95%) showed no changes in any of the measures of quality of life, behaviour, depression or executive function after 24 weeks of treatment. The exception was mean Child Health Questionnaire physical summary scores, which declined from baseline, indicating worse physical aspects of quality of life; 15% experienced a clinically significant decline and no patients experienced a clinically significant improvement ($p=0.013$ for changes in mean scores). However, after 1 or 2 years of follow-up, none of the children and young people who completed 48 weeks of treatment showed differences from baseline ($p>0.05$) for any of the quality-of-life outcome measures.

- 4.1.15 None of the 5 studies of peginterferon alfa-2b reported health-related quality-of-life outcomes.

Assessment Group's critique of Roche's clinical-effectiveness submission

- 4.1.16 According to the Assessment Group, Roche did not conduct a systematic review of clinical effectiveness. The bibliographic databases and search strategies provided by the manufacturer were not sufficiently detailed to permit the Assessment Group to reproduce the evidence. Roche provided clinical-effectiveness results primarily from Schwarz et al., Sokal et al. and 2 other uncontrolled trials, which did not meet the inclusion criteria for the decision problem because 1 study had a population older than that specified in the scope and the other study was retrospective and did not provide details of peginterferon dose or treatment duration. The Assessment Group commented that Roche did not report the methods it used to screen, extract or quality assess the literature.
- 4.1.17 The Assessment Group noted that Roche reported comparative data for both arms of the study by Schwarz et al., even though peginterferon alfa-2a monotherapy is outside the marketing authorisation and scope. The Assessment Group noted that the proportion of patients with a sustained virological response in Roche's submission were comparable with those seen in the assessment report. Roche did not report virological outcomes during treatment or health-related quality of life. Effects of treatment on weight, height and growth were reported only from the studies excluded from the Assessment Group's evaluation. Roche concluded that the evidence demonstrated that peginterferon alfa-2a plus ribavirin was effective compared with best supportive care for all genotypes.

4.1.18 The Assessment Group commented that, although Roche stated in its submission that there was no safety concern with regard to adverse reactions to peginterferon alfa-2a, it reached this conclusion using data only from the Schwarz et al. study, in which both treatment arms received peginterferon alfa-2a.

Assessment Group's critique of Merck Sharp and Dohme's clinical-effectiveness submission

4.1.19 MSD's submission reported a systematic review of clinical effectiveness that included 8 studies, but only presented study characteristics for 5. Of the 8 studies, 6 were among the Assessment Group's 7 studies: 4 for peginterferon alfa-2b (Al Ali et al., Jara et al., Pawlowska et al., Wirth et al.) and 2 for peginterferon alfa-2a (Schwarz et al., Sokal et al.). Of the studies included in the manufacturer's submission but excluded from the assessment report, 1 had included patients older than the age range specified in the scope and the other included patients who had previously received non-pegylated interferon. The MSD submission did not include the Ghaffar et al. study included in the assessment report.

4.1.20 MSD's submission included data on growth inhibition and adverse events, and a meta-analysis that pooled data for sustained virological response, virological response at 24 weeks, relapse, discontinuation of treatment and selected adverse events. The Assessment Group commented that the sustained virological response rates included in MSD's submission were comparable with those in the assessment report, and that there was moderate to substantial heterogeneity in the meta-analyses (and therefore the interpretation of the results was unclear). MSD concluded that both peginterferon alfa-2a plus ribavirin and peginterferon alfa-2b plus ribavirin were effective compared with best supportive care, and that there were no clear differences between treatments.

4.2 Cost effectiveness

- 4.2.1 The Assessment Group systematically reviewed existing economic evaluations of peginterferon alfa-2a and peginterferon alfa-2b treatment in children and young people with chronic hepatitis C. It identified a conference abstract and a paper, but neither met its criteria for inclusion.
- 4.2.2 The Assessment Group also systematically reviewed the literature on health-related quality of life of people with chronic hepatitis C to populate the economic model with health-state utility values and calculate quality-adjusted life years (QALYs). It restricted searches to studies using EQ-5D. The Assessment Group identified 2 published studies (Bjornsson et al. 2009, Chong et al. 2003) performed in adults with chronic hepatitis C in Sweden and Canada, but found no studies in children. The Assessment Group concluded that the estimates were sufficiently robust to use in its economic evaluation.

Roche's economic model for peginterferon alfa-2a plus ribavirin

- 4.2.3 Roche submitted an economic evaluation using a Markov model with a structure similar to other models used to evaluate treatments for chronic hepatitis C in adults. Roche compared the costs and health outcomes of treatment with peginterferon alfa-2a plus ribavirin with best supportive care (no drug treatment). Roche's model extrapolated the health effects of peginterferon alfa-2a plus ribavirin in children and young people with hepatitis C reflecting the population characteristics of the clinical trials over a 30-year time horizon. Children enter the model at an average age of 11 years in a model state of mild or moderate hepatitis C-related fibrosis (88% and 12% respectively), based on the weighted average of children and young people participating in the peginterferon alfa-2a studies. Children and young people with HCV genotype 1, 4 or 5 whose

disease has responded to treatment with peginterferon alfa-2a plus ribavirin at 24 weeks receive treatment for 48 weeks. Children and young people with HCV genotype 2 or 3 are split into 2 groups to compare 24 weeks of treatment with 48 weeks of treatment. One group receives treatment for 24 weeks only and the other for 48 weeks (if their hepatitis C responds to treatment at 24 weeks). If treatment does not result in a sustained virological response, children and young people remain in their current health state or 'progress' to mild hepatic fibrosis, moderate hepatic fibrosis, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma (liver cancer), liver transplantation or death. For transitions to decompensated cirrhosis, hepatocellular carcinoma and liver transplantation, Roche used transition probabilities from adults used in previous appraisals for chronic hepatitis C. Roche assumed that the mortality risks for those in the sustained virological response, mild hepatic fibrosis, moderate hepatic fibrosis and compensated cirrhosis states were the same as in the general population. Roche assumed that the mortality risks for people in the decompensated cirrhosis, hepatocellular carcinoma and liver transplantation states were similar to those of people with chronic liver disease.

- 4.2.4 Roche's model also included a probability of spontaneous sustained virological response in untreated children: an annual probability of 2.37% for children with maternally transmitted HCV within the first 5 years and an annual probability of 1.65% for children with HCV acquired by other means. Based on the studies identified by Roche, 70% of children have maternally transmitted HCV and 30% have non-maternally transmitted HCV. Roche assumed that the most common adverse reactions seen in the studies, such as flu-like illness, chest infections, headache, and gastrointestinal and skin disorders, would impact on health-related

quality of life, but not on costs. Roche did not include depression related to peginterferon alfa-2a as an adverse reaction in the economic model. It assumed that the disutility from treatment with peginterferon alfa-2a was equal to treatment with non-pegylated interferon, as seen in the Wright et al. (2006) study in adults.

4.2.5 Roche's base-case analysis considered treatment-naive children and young people, as reflected in the peginterferon alfa-2a studies and in accordance with the UK marketing authorisation. Roche also presented an analysis for a subgroup of patients whose disease does not respond to treatment and who are re-treated. The model evaluated costs from the perspective of the NHS and personal social services. Costs and health outcomes were discounted at a rate of 3.5% per annum, in accordance with the NICE reference case.

4.2.6 Roche estimated the clinical effectiveness of treatment in the base case according to the weighted average percentages of patients who had a sustained virological response in the Schwarz et al. study and 3 uncontrolled studies: 59% for genotypes 1, 4, 5 and 6 with 48 weeks of treatment and 89% for genotypes 2 and 3 with 24 weeks of treatment. Roche included the cost of peginterferon alfa-2a and ribavirin, as well as the cost of evaluating and monitoring patients. Administration costs were not included. The drug doses depended on age, body surface area and weight, and the base-case model assumed an average dose corresponding to the dosing regimen of the population in the Schwarz et al. trial using an age-related mean height and weight from the Health Survey for England 2010. In the base case, the estimated costs for 48 weeks of combination therapy were £8307. Roche assumed that patients do not share vials.

- 4.2.7 Roche assumed that children and young people who have a sustained virological response would not incur any further costs related to chronic hepatitis C. Roche performed sensitivity analyses using assumptions from previous appraisals in which sustained virological response costs were £335 and follow-up surveillance costs for children and young people whose hepatitis C has responded in the first year were £165.
- 4.2.8 For children and young people younger than 17 years, Roche applied a baseline utility of 0.95 in line with a study by Saigal et al. (1994). For the healthy population aged 17 years and older, the model applied utility values for adults, derived using an algorithm developed by Ara and Brazier (2009), in line with the EQ-5D derived utility weights used in previous health technology assessments for adults with chronic hepatitis C. The mean utility value for sustained virological response after mild disease was 0.83, whereas the utility weight for having mild disease was 0.77 and for receiving peginterferon treatment for mild disease was 0.66. The mean utility value for moderate liver disease was 0.66 and for receiving treatment for moderate disease was 0.55, compared with 0.55 for compensated cirrhosis, 0.45 for either decompensated cirrhosis or hepatocellular carcinoma and 0.67 after liver transplantation.

Results of Roche's economic model

- 4.2.9 The cost-effectiveness result for Roche's base-case population for peginterferon alfa-2a plus ribavirin compared with best supportive care was £3914 per QALY gained for children and young people with HCV genotype 1, 4 or 5. Peginterferon alfa-2a plus ribavirin dominated (that is, was less costly and more effective than) best supportive care for children and young people with HCV genotype 2 or 3. The results from Roche's cost-effectiveness acceptability curves for its base-case populations showed that the probability

that peginterferon alfa-2a plus ribavirin treatment was cost effective compared with best supportive care at £20,000 per QALY gained for children and young people with HCV genotype 1, 4 or 5 treated for 48 weeks was 91.6%, and for children and young people with HCV genotype 2 or 3 treated for 24 weeks was 97.2%.

- 4.2.10 Roche performed one-way and two-way deterministic analyses and found that the results were most sensitive to the time horizon, rate of disease progression, probability that a patient had a sustained virological response with treatment, liver disease at baseline, the value of the health-state utilities and annual cost of achieving sustained virological response. The cost effectiveness of peginterferon alfa-2a compared with best supportive care remained below £13,000 per QALY gained for all analyses.

Merck Sharp and Dohme's economic model for peginterferon alfa-2b plus ribavirin

- 4.2.11 MSD submitted a de novo economic evaluation based on previously published economic evaluations of the treatment of chronic hepatitis C in adults. It compared the costs and health outcomes of peginterferon alfa-2a plus ribavirin and peginterferon alfa-2b plus ribavirin for treating children and young people aged 3–17 years compared with best supportive care. The base-case economic analysis included previously untreated children and young people aged 5–17 years without HIV co-infection. Because peginterferon alfa-2b has a marketing authorisation that also includes children aged 3–4 years, MSD conducted an additional subgroup analysis in this age group. It used a Markov model that follows a hypothetical cohort over a lifetime time horizon (up to age 100 years). People enter the model in the mild hepatitis C, moderate hepatitis C or compensated cirrhosis states and receive treatment in cycle 1 for 12, 24 or 48 weeks depending on stopping rules (whether a patient's disease responds during treatment) and

genotype. The modelled health states are: mild liver fibrosis, moderate liver fibrosis, compensated cirrhosis of the liver, decompensated cirrhosis of the liver, hepatocellular carcinoma (liver cancer), liver transplantation or death. MSD used child-specific probabilities for transitions between the mild and moderate fibrosis states, and the moderate fibrosis and compensated cirrhosis states. Transition probabilities from studies in adults were used for more advanced hepatitis C health states. MSD assumed that the mortality risks for people in the sustained virological response, mild liver fibrosis, moderate liver fibrosis and compensated cirrhosis states were the same as for the general population. MSD assumed that children and young people in the decompensated cirrhosis, hepatocellular carcinoma and liver transplantation states have a higher mortality risk than the general population.

- 4.2.12 MSD's base-case analysis considered treatment-naive children and young people using data from peginterferon alfa-2b studies and in accordance with the UK marketing authorisation for peginterferon alfa-2b. The model evaluated costs from the perspective of the NHS and personal social services. Costs and health outcomes were discounted at a rate of 3.5% per annum, in accordance with the NICE reference case.
- 4.2.13 MSD modelled parameters reflecting the clinical effectiveness of peginterferon alfa-2a and -2b plus ribavirin in the base case, using calculated weighted averages of the percentage of patients who had a sustained virological response from 8 trials (section 4.1.19). MSD included the costs of peginterferon alfa-2a and -2b plus ribavirin, of investigations, and of monitoring during and after treatment. MSD did not include costs associated with treating adverse events, noting the precedent of [Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C \(part review of](#)

[NICE technology appraisal guidance 75 and 106](#)) (NICE technology appraisal 200). Dosing depended on age, body surface area and weight. The average ages at model entry were 7 years (age 5–8 years; 30.8%), 11 years (age 9–13 years; 38.5%) and 16 years (age 14–17 years; 30.8%) and there was an equal distribution of males and females. For body weight and height, MSD derived its estimates from mean values from the UK World Health Organisation growth charts for 2009 and UK 1990 standard centile charts presented in BNF 63. MSD assumed that patients do not share vials.

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 children and young people 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 children and young people 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. Child-specific costs for resource use and monitoring while on treatment, including follow-up visits after the completion of treatment, were also included in the model.

4.2.15 Because there is no published evidence on health-related quality of life for children and young people with chronic hepatitis C, MSD used values for its economic analysis from previous NICE technology appraisals of adults with chronic hepatitis C. The utility values for patients with mild hepatitis C were elicited using the standard EQ-5D time trade-off tariff from people with hepatitis C (Wright et al). The disutility value for treatment-emergent adverse

reactions was also derived from this trial. People receiving peginterferon alfa-2b plus ribavirin had a utility value of 0.77 at baseline and 0.66 when assessed at 12 and 24 weeks after starting treatment. MSD applied the resulting reduction in utility of 0.11 to all patients receiving peginterferon alfa-2b in the model regardless of disease severity. MSD obtained utility values for patients with moderate and compensated cirrhosis from a multicentre observational study involving 302 patients with severe liver disease associated with chronic hepatitis (reported in Wright et al.). For the remaining health states, MSD used utility values from a prospective multicentre study by Longworth et al. (2004) assessing health-related quality of life before and after liver transplant in the UK.

Results of Merck Sharp and Dohme's economic model

4.2.16 The cost-effectiveness results for MSD's base-case population (age 5–17 years) suggested that both types of peginterferon alfa (2a and 2b) plus ribavirin dominated best supportive care, that is, were more effective and cost less. MSD obtained a similar result for children aged 3–4 years. Both types of peginterferon alfa (2a and 2b) plus ribavirin dominated best supportive care for all genotypes. Peginterferon alfa-2b dominated peginterferon alfa-2a in the base-case analysis (all ages, –£3397 per QALY gained) and in all subgroup analyses, except in children and young people aged 9–13 years, and in children and young people with HCV genotypes 1 or 4. MSD conducted deterministic sensitivity analyses around structural assumptions (time horizon, discount rates) and the modelled parameter values. The deterministic sensitivity analyses showed that peginterferon alfa-2b dominated best supportive care in most scenarios, except in those in which MSD varied the time horizon, assumed efficacy and discount rates.

Assessment Group's critique of the cost-effectiveness analyses by Roche and Merck Sharp and Dohme

- 4.2.17 The Assessment Group critiqued the Roche and MSD submissions and considered that the economic models met all of the requirements for methodological quality and generalisability, except that neither manufacturer provided evidence that its model had been validated.
- 4.2.18 Roche and MSD used the state-transition model applied in previous health technology assessments of peginterferon alfa treatments in adult populations, which the Assessment Group considered appropriate, commenting that most of the time spent in the model would be after treatment as an adult, rather than as a child. Because most children and young people start treatment (and enter the model) with mild chronic hepatitis C, few will progress to more severe health states before they become adults. Therefore, the Assessment Group considered that health-state transition values from adults used in the manufacturers' models were appropriate.
- 4.2.19 Both Roche and MSD conducted literature reviews to estimate the transition probabilities from mild-to-moderate and moderate-to-compensated cirrhosis health states. The transition probability for mild-to-moderate hepatitis C was 0.014 per cycle in both manufacturers' submissions, whereas the transition probabilities for moderate hepatitis C to compensated cirrhosis differed for Roche (0.021) and MSD (0.0038) and for the Assessment Group (see section 4.2.29).
- 4.2.20 The manufacturers' models used different time horizons: Roche used a time horizon of 30 years and MSD used a lifetime horizon. Another difference between the manufacturers' models was that Roche assumed that some patients have a spontaneous sustained virological response (that is, without treatment) in its base-case,

whereas MSD only tested this assumption in a sensitivity analysis. The Assessment Group commented on the small (less than 3%) probability of spontaneous sustained virological response assumed by Roche, noting it was unlikely to affect the cost-effectiveness results. Both manufacturers applied the same health-state utility values used in previous adult chronic hepatitis C models except for the values for sustained virological response in the mild disease state, which were almost identical in both submissions (0.83 and 0.82 Roche and MSD respectively). Roche did not provide utility values for having a sustained virological response in the moderate disease or compensated cirrhosis health states. Most health-state costs used in the manufacturers' submissions were similar or the same.

Assessment Group's economic model

4.2.21 The Assessment Group developed an economic model estimating the cost effectiveness of peginterferon alfa-2a and peginterferon alfa-2b (both plus ribavirin) for treating chronic hepatitis C in children and young people compared with each other and with best supportive care. The model converted the probability of sustained virological response (the definition of treatment effectiveness) to long-term survival outcomes from the systematic review. The perspective of the analysis was that of the NHS and personal social services. The model time horizon was 70 years and the cycle length was 1 year. The costs and benefits were discounted at 3.5% per year, in accordance with the NICE reference case. Costs were taken from the most recently available data (2011–12). The Assessment Group confirmed the functionality of its model by checking the structure, calculations and data inputs.

4.2.22 The Assessment Group adapted models used in [Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C \(extension of technology appraisal guidance 75\)](#) (NICE technology appraisal

106) and [Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C \(part review of NICE technology appraisal guidance 75 and 106\)](#) (NICE technology appraisal 200), which assessed chronic hepatitis C in adults. The Assessment Group modified the structure of the model to include health states for the different levels of fibrosis (F0–F4, METAVIR scoring system), instead of the health states of mild hepatitis C, moderate hepatitis C and compensated cirrhosis. It did this based on evidence from Thein et al. (2008), which reviewed published rates of progression specific to stages of fibrosis progression rates based on 111 studies of people with chronic hepatitis C (n=33, 121). In the model, people with chronic hepatitis C with a METAVIR score between F0 and F3 or compensated cirrhosis (F4) can have a sustained virological response; remain in their current health state; or progress to more severe stages of liver disease. The Assessment Group assumed that a person who has a sustained virological response does not experience a relapse. It also assumed that people who have a sustained virological response or chronic hepatitis C with a METAVIR score between F0 and F4 have the same mortality risk as the general population, whereas people with decompensated liver disease, hepatocellular carcinoma and those who undergo liver transplantation have higher mortality risks.

- 4.2.23 The Assessment Group incorporated most of the assumptions made in the models used in previous technology appraisals for chronic hepatitis C in adults, including: that a person's disease state before treatment influences the subsequent risk of progressive liver disease and health-related quality of life; that a person who does not have a sustained virological response has the same risk of disease progression as a person who does not receive treatment; that a person with mild or moderate hepatitis C and compensated cirrhosis has the same probability of having a

sustained virological response; that the model excludes the rare possibility of having to stop treatment because of adverse reactions; and that the model excludes costs associated with managing adverse reactions because they are unlikely to be substantial. After discussion with experts, the Assessment Group further assumed that no patient would have a sustained virological response spontaneously (that is, without treatment); that a patient with genotype 1 or 4 HCV stops treatment at 24 weeks if there is no virological response by week 12; and that it would be acceptable to include transition probabilities, utility weights and health-state costs from adults in the model. Although the Assessment Group noted that a child's hepatitis C can affect parents' or carers' quality of life, it did not find sufficient evidence to include it in the model. The Assessment Group commented that stigma associated with hepatitis C may lower the quality of life of children and young people; however, the data were sparse.

- 4.2.24 The Assessment Group used the baseline characteristics of the populations from the clinical trials in its model including the distribution across METAVIR stages of chronic hepatitis C of 24.6% at stage F0 (no fibrosis), 66.2% at stage F1 (portal fibrosis with no septa), 7.1% at stage F2 (portal fibrosis with few septa), 2.1% at stage F3 (septal fibrosis with no cirrhosis) and 0 at stage F4 (compensated cirrhosis).
- 4.2.25 For utility values and health-state costs, the Assessment Group used values from previous technology appraisals so that F0 and F1 corresponded to the mild, and F2 and F3 to the moderate, hepatitis C health states. The Assessment Group searched for new evidence related to the natural history of hepatitis C in children or young people, but found none.

Results of Assessment Group's economic model

- 4.2.26 The Assessment Group's probabilistic cost-effectiveness results for the base-case population suggested that both peginterferon alfa-2a and peginterferon alfa-2b dominated best supportive care because they were less expensive and more effective. Treatment was more effective for genotype 2 or 3 than for genotype 1 or 4.
- 4.2.27 The Assessment Group's base-case results for peginterferon alfa-2a compared with peginterferon alfa-2b showed that peginterferon alfa-2a cost less (£19,055 compared with £20,371) and was more effective than peginterferon alfa-2b (22.25 QALYs compared with 22.19 QALYs). For people with genotype 1 or 4, peginterferon alfa-2a was also less costly and more effective than peginterferon alfa-2b (£21,278 compared with £22,316; 22.00 QALYs compared with 21.97 QALYs). However, for people with genotype 2 or 3, peginterferon alfa-2a cost more and was less effective than peginterferon alfa-2b (£11,831 compared with £11,202; 23.05 QALYs compared with 23.21 QALYs). The Assessment Group stated that the estimates of clinical effectiveness were key drivers of the differences in costs and outcomes between peginterferon alfa-2a and peginterferon alfa-2b within the model.
- 4.2.28 The Assessment Group performed one-way deterministic sensitivity analyses investigating the effect of uncertainty on the cost-effectiveness results varying the time horizon (30 years and 90 years); discount rate (0% discount for both costs and outcomes, 6% discount for costs with 1.5% discount for outcomes, 1.5% discount for both cost and outcomes, and 6% for both cost and outcomes); the proportions of people who had a sustained virological response with peginterferon alfa-2a (69% and 51%) and with peginterferon alfa-2b (65% and 52%); degree of liver fibrosis (100% F0, 100% F2, 100% F3 and 20% F4); starting age (5 years

and 16 years); transition probabilities (lower confidence interval [CI] and upper CI); utility values (lower CI, upper CI and from previous appraisal); and health-state costs (lower CI and upper CI). In all analyses, both peginterferon alfa-2a plus ribavirin and peginterferon alfa-2b plus ribavirin dominated best supportive care. The analyses showed that the model was most sensitive to changes in the discount rate chosen and the time horizon. 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). However, 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.

4.2.29 The Assessment Group also conducted scenario analyses. In 1 scenario analysis, it varied the transition probabilities between the chronic hepatitis C health states (F0–F3) to the decompensated cirrhosis health state (F4), varying the transition probabilities from 0.1 (used in the base case) to between 0.05 and 0.3, with the same probability applied for transitions between each of the states from F0 to F4. Peginterferon alfa-2a dominated best supportive care for all transition probabilities used in the scenario analysis to a lesser or greater extent depending on the amount of time spent in the chronic hepatitis C state. Another scenario analysis assessed the impact of delaying peginterferon alfa-2a treatment until age 18–30 years instead of starting it during childhood. This ‘watchful waiting’ strategy was associated with slightly higher costs (between £21,959 and £26,668) and slightly reduced QALYs (between 22.22 and 21.79 QALYs) compared with treatment during childhood

(£19,055 and 22.25 QALYs for the base case). The Assessment Group commented that the conclusions made in scenarios 2 and 3 would also apply to peginterferon alfa-2b compared with best supportive care.

- 4.2.30 The Assessment Group conducted probabilistic sensitivity analysis for the following parameters: the proportion of children and young people with a given genotype, transition probabilities, health-state utilities and costs associated with monitoring, health states and treatment. The results of the probabilistic sensitivity analysis closely reflect the results of the deterministic base case. The probabilities that peginterferon alfa-2a and -2b are cost effective at £20,000 and £30,000 per QALY gained were 68% and 66% for peginterferon alfa-2a, and 32% and 34% for peginterferon alfa-2b, respectively.

Comparison of the Assessment Group and manufacturers' models

- 4.2.31 The Assessment Group compared its results with those of the manufacturers. It commented that all 3 models found that peginterferon alfa-2a and peginterferon alfa-2b (each plus ribavirin) dominated best supportive care. MSD and the Assessment Group also compared peginterferon alfa-2a with peginterferon alfa-2b. The Assessment Group's results, which suggested that peginterferon alfa-2a dominated peginterferon alfa-2b, differed from those of MSD, which suggested that peginterferon alfa-2b dominated peginterferon alfa-2a. The Assessment Group suggested caution when interpreting these results because the differences were marginal. The costs and QALY estimates used in each evaluation varied. The differences in costs were based on the use of a shorter time horizon (Roche) or the length of time spent in chronic hepatitis C health states (shorter in the Assessment Group's analysis compared with MSD's). The differences in QALY estimates were based on the use of a shorter time horizon (Roche) and the lower

utility values used (MSD) compared with the Assessment Group's model.

Innovation

4.2.32 Roche commented that pegylated interferons have existed for over 15 years, so it does not consider pegylated interferon to be an innovative medicine, but instead is an option available to physicians, patients and carers when considering treatments for chronic hepatitis C. By contrast, MSD considered that peginterferon alfa (2a and 2b) plus ribavirin were innovative therapies for treating chronic hepatitis C in adults when first launched and that extending the marketing authorisation to children and young people means that this innovation now applies to younger patients. In addition, peginterferon alfa-2a and peginterferon alfa-2b are dosed once weekly, compared with the 3-times weekly dosing of interferon alfa, therefore reducing the burden of the treatment.

4.2.33 MSD believes that successfully treating chronic hepatitis C in children and young people will affect parents and carers, and this would not be captured in calculating the QALY. MSD cited a study reporting that hepatitis C among children and young people is associated with increased carer stress, and a study conducted in Australia indicating substantial quality-of-life benefits for parents and carers when the child has a sustained virological response.

4.2.34 MSD also commented that children and young people with chronic hepatitis C who have a sustained virological response do not infect others with the virus, and this reduces the risk of onward transmission of HCV in the UK.

4.3 Consideration of the evidence

4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of peginterferon alfa-2a plus ribavirin

and peginterferon alfa-2b plus ribavirin, having considered evidence on the nature of chronic hepatitis C in children and young people and the value placed on the benefits of technologies by people with the condition, their families and carers, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

Clinical effectiveness

4.3.2 The Committee heard from the clinical specialists that both peginterferon alfa-2a and peginterferon alfa-2b (each plus ribavirin) are currently used to treat some children and young people with chronic hepatitis C in the UK. The clinical specialists confirmed that the 2 peginterferons are considered equivalent in their mechanism of action and clinical efficacy; however, peginterferon alfa-2b is prescribed more frequently because it can also be given to children who are aged 3–4 years. 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 infection is contracted and therefore how likely a spontaneous sustained virological response is without treatment. The Committee heard that children aged 3 years or younger, or those who contract HCV infection through a blood transfusion, are more likely to have a spontaneous sustained virological response during the acute infection phase than those who are aged 4 years and older or who have contracted the infection from their mother at birth and are in the chronic phase. The Committee recognised that the decision to treat with either regimen would largely be determined by clinical judgement and the specifics of the marketing authorisation.

4.3.3 The Committee considered the impact that difficult family circumstances, such as parents who misuse drugs, may have on the ability of children and young people to adhere to treatment. It

heard that clinical specialists do not recommend treating children and young people and their mothers (if they also have hepatitis C) at the same time because the adverse reactions of treatment for each might affect adherence. The clinical specialists indicated that support for children and young people and their families is not routinely available from adult hepatology centres and, to adhere to treatment, children and young people need specialised support, which is only available in some specialist hepatology centres in England and Wales. The Committee noted that families living away from a specialist centre would have the burden of travelling for treatment and monitoring. The Committee concluded that, although the timing of treatment is important, and better health outcomes are more likely if support is provided to ensure adherence to treatment, how to manage the disease is ultimately the decision of parents or carers, and the child or young person, together with clinicians,.

- 4.3.4 The Committee considered the evidence presented on the proportion of children and young people with chronic hepatitis C who have a sustained virological response after treatment with peginterferon alfa plus ribavirin. It acknowledged the paucity of relevant studies in children and young people identified by the manufacturers and the Assessment Group, and noted that these studies had enrolled few patients and were generally of poor quality. In addition, because the evidence base largely comprised single-arm studies that did not have any control groups which did not receive therapy, the Committee would have expected the manufacturers' and Assessment Group's submissions to have provided supporting data from adult trials to establish the efficacy of peginterferon alfa (2a and 2b) plus ribavirin. The Committee was aware that having a lower viral load or milder degree of liver damage at the start of treatment increases the likelihood of a sustained virological response. Despite the limitations of the clinical

evidence and the lack of comparative evidence, the Committee concluded that peginterferon alfa (2a and 2b) plus ribavirin is an effective therapy in children and young people with chronic hepatitis C across all genotypes.

4.3.5 The Committee discussed the generalisability of the trial results to the UK population and heard from the clinical specialists that the average age of entry into the trials (age 11 years) reflects the average age of children and young people currently treated in the UK, although it was noted that, in the future, patients will be treated at a younger age once newer therapies become available. The Committee also heard from the clinical specialists that some children clear the virus spontaneously without treatment, but that the proportion that do is considerably lower than the proportion that cleared the virus when treated in the single-arm studies. The Committee was satisfied that the trial results were largely generalisable to the UK population.

4.3.6 The Committee queried whether there were any subgroups in which treatment with peginterferon alfa plus ribavirin would be most clinically effective, whether there were groups in which clinicians chose to 'watch and wait' rather than to treat, and if there was a general acceptance in the clinical community about the 'best' time to treat chronic hepatitis C. The clinical specialists stated that children and young people with interleukin-28 (IL-28) gene polymorphism were more likely to clear HCV with or without treatment, but that testing for IL-28 is not routinely performed in UK clinical practice. The Committee heard from the clinical specialists that obesity is an increasing problem in children and young people and although it has been linked with a lower probability of having a sustained virological response, it is not currently a factor that precludes patients from having treatment. With respect to the timing of treatment, the Committee heard from the clinical

specialists that, because younger children have lower baseline viral loads and less liver damage, both of which improve the response to treatment, treating early was better than treating later in adolescence or adulthood. The Committee also heard that before the age of 10 years a child's immune system mounts less of an inflammatory response to HCV, and that this period precedes the pubertal growth spurt; therefore, treatment given at this time reduces the possible negative impact on a child's growth rate. Additionally, because young children have fewer comorbidities and generally do not consume alcohol, they have fewer complications associated with liver disease and therefore are more likely to have favourable outcomes following treatment. The Committee heard from the clinical specialists that another benefit of treating a child early is that he or she may not remember the treatment itself or even ever having had hepatitis C. The Committee concluded that clinical experience supported early treatment, but that 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.

- 4.3.7 The Committee considered how likely it is that children and young people with a sustained virological response will remain free from HCV; that is, how likely it is that they will be 'cured'. It understood that 95% of children and young people treated before the onset of significant liver disease and who have a sustained virological response remain free from HCV for the rest of their lives. The Committee heard from the clinical specialists that people do not generally undergo repeat liver biopsies after treatment has been completed, but studies showed that children and young people with sustained virological responses remained healthy in the following 5 years. It noted however that these studies were small and not necessarily representative of the UK population; therefore the Committee would have expected to have been presented with data

from trials in adults with HCV to augment the evidence related to the likelihood of a long-term response in children and young people after treatment with peginterferon alfa plus ribavirin. Nevertheless, the Committee concluded that it was plausible that a sustained virological response achieved in childhood or adolescence could last throughout a person's lifetime.

4.3.8 The Committee was aware that the population identified in the scope specified children and young people who have not previously been treated for HCV. It heard that clinicians do not offer re-treatment to children and young people previously treated with peginterferon plus ribavirin. Instead, when treatment has not resulted in a sustained virological response, these children and young people might be enrolled in a clinical trial of a newer technology or offered further treatment options (such as boceprevir or telaprevir) from 18 years of age, in line with guidelines for the treatment of adults with chronic hepatitis C. The Committee was reassured by the clinical specialists that children and young people would be treated only once with peginterferon alfa plus ribavirin, if it was recommended for routine use in UK clinical practice.

4.3.9 The Committee considered the adverse reactions of treatment with peginterferon alfa plus ribavirin. It heard that the main adverse reactions are: severe psychiatric and central nervous system effects, particularly depression, suicidal ideation and attempted suicide, weight loss and growth inhibition. The Committee heard from the patient expert that the patient community had documented aggressive behaviour possibly attributable to ribavirin. However, such aggressive behaviour was attributed by the manufacturers to peginterferon alfa, not ribavirin. The manufacturers and the clinical specialists explained that, without studies that compare treatment with peginterferon alfa with and without ribavirin, it was sometimes difficult to separate the adverse reactions of peginterferon alfa from

those of ribavirin. The Committee was aware that the Schwarz et al. study made this comparison, but these data were not presented to the Committee. The Committee also heard that other important adverse reactions associated with treatment are slowed growth and weight loss, both of which are of particular concern during the pubertal growth period. The clinical specialists explained that 48 weeks of treatment with peginterferon alfa plus ribavirin during this period can result in a small reduction in expected height and, while some studies have shown that growth resumes after treatment, some children and young people do not return to their pre-treatment growth percentile. The Committee acknowledged advice from the clinical specialists that, if a decision is made to delay treatment beyond puberty, clinicians would monitor the patient's condition and, if it worsens, treatment options would be re-evaluated. The Committee concluded that, although treatment with peginterferon alfa plus ribavirin may impair growth, the possibility of progressive liver disease without treatment outweighs the problems associated with being slightly shorter.

- 4.3.10 The Committee considered whether there is a stigma associated with hepatitis C in children and young people. The clinical specialists and patient experts expressed the opinion that a stigma associated with hepatitis C does exist, in part related to its association with intravenous drug misuse. The Committee heard that children and young people with hepatitis C have more difficulty being placed with foster parents because of largely unfounded fears that the virus will be transmitted to other family members and also because of possible psychological effects associated with treatment. The Committee concluded that hepatitis C was associated with a stigma, and early successful treatment would lessen the stigma later in life.

4.3.11 The Committee considered whether peginterferon alfa (2a and 2b) plus ribavirin were innovative technologies for treating hepatitis C in children and young people. It was aware that, when first introduced for adults, both peginterferons were likely to have been innovative treatments. However, the Committee concluded that, although peginterferon alfa plus ribavirin represented a useful treatment option for children and young people with chronic hepatitis C, the technologies themselves could no longer be considered innovative for the purpose of this evaluation, since they had already been used successfully in adults.

Cost effectiveness

4.3.12 The Committee considered the Assessment Group's and the 2 manufacturers' economic models. It noted that:

- The Assessment Group's and MSD's cost-effectiveness results for their respective base cases showed that peginterferon alfa plus ribavirin was more effective and less costly than best supportive care across all genotypes.
- Roche's cost-effectiveness modelling resulted in an incremental cost-effectiveness ratio (ICER) for peginterferon alfa plus ribavirin of £3900 per QALY gained compared with best supportive care in children and young people with HCV genotype 1, 4 or 5. Peginterferon alfa plus ribavirin dominated best supportive care in children and young people with genotype 2 or 3.
- When comparing the 2 peginterferons, the Assessment Group's base case showed that peginterferon alfa-2a dominated peginterferon alfa-2b, whereas MSD found that peginterferon alfa-2b mainly dominated peginterferon alfa-2a.

4.3.13 The Committee noted that the stopping rules differed between both the manufacturers' submissions and the Assessment Report

(section 4.2.3 [Roche], 4.2.11 [MSD], and 4.2.23 [Assessment Group]). It was aware that, according to the summary of product characteristics for peginterferon alfa-2a, patients infected with HCV genotype 2 or 3 should receive 24 weeks of treatment, whereas patients infected with any other genotype should receive 48 weeks of therapy unless they have detectable levels of HCV RNA despite an initial 24 weeks of therapy, at which point they should stop therapy because it is unlikely they will have a sustained virological response with continued therapy. The Committee heard from the clinical specialists that, in practice, children and young people with genotype 2 or 3 are evaluated for an early virological response at 12 weeks, although they generally continue to receive treatment for 24 weeks. Children and young people with genotype 1 or 4 are encouraged to stop treatment at 24 weeks if there has not been a virological response, although some parents prefer their children to continue treatment for the full 48 weeks regardless of initial response. The Committee would have expected the stopping rules to be consistent with clinical practice and the marketing authorisation of both products but concluded that, although the stopping rules varied across the models, the uncertainty associated with this was unlikely to alter the conclusions about the cost effectiveness of either of the peginterferons compared with best supportive care.

- 4.3.14 The Committee discussed whether, for patients who do not have a sustained virological response to peginterferon alfa plus ribavirin, subsequent treatment in adulthood with the second-generation technologies boceprevir (see [Boceprevir for the treatment of genotype 1 chronic hepatitis C](#) [NICE technology appraisal 253]) and telaprevir (see [Telaprevir for the treatment of genotype 1 chronic hepatitis C](#) [NICE technology appraisal 252]) should have been included in the economic models. It was concerned that none

of the economic evaluations included re-treatment options for young people reaching 18 years of age, and noted that the impact of the future costs of these technologies in the model is uncertain. The Committee acknowledged that, despite this limitation, the results were largely robust to changes in variables within the model and therefore it was satisfied that the omission of the costs of future technologies in the model would not greatly affect conclusions about the cost effectiveness of peginterferon alfa plus ribavirin. The Committee, however, stated that it would expect future economic evaluations of treatments for children and young people with HCV to take into account the use of technologies currently licensed for adults and recommended as an option by NICE when re-treatment is required in adulthood.

- 4.3.15 The Committee noted that the utility values used in the models were based on previous technology appraisals in adults with chronic hepatitis C, and that they had not been updated, or revalidated to assess their appropriateness for an appraisal of treatments in a younger population. The Committee stated that it would have expected more detailed information about the source and validation of utility values relied on in the manufacturers' submissions. The Committee heard that the Assessment Group related the health states used in previous technology appraisals in adults with chronic hepatitis C to the METAVIR system and conducted searches to identify new evidence related to the natural history of hepatitis C in children or young people, but found no new data. It also noted that the Assessment Group relied on published utility values derived from the health-related quality of life of adults with chronic hepatitis C in Sweden and Canada to populate its economic model. The Assessment Group told the Committee that it chose these data because they were more recent than values used in previous hepatitis C technology appraisals and were based on

larger sample sizes. The Committee questioned the manufacturers' and Assessment Group's choice of utility values and stated their preference for utility values derived from UK population studies. Although the Committee remained uncertain about what effect alternative utility values would have on the cost-effectiveness results, it agreed that an exploration of alternative utility values would not affect conclusions about the cost effectiveness in this appraisal.

4.3.16 The Committee considered the conflicting opinions in the manufacturers' submissions and the Assessment Report on whether some people can have a spontaneous sustained virological response without treatment. 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 both considered the impact of assuming a spontaneous sustained virological response in sensitivity analyses. The Committee heard from the clinical specialists that a spontaneous sustained virological response would probably only occur before the age of 4 years or during the acute phase of HCV infection. The Committee concluded that addressing the impact of a spontaneous sustained virological response on the ICERs would not greatly affect the conclusions about the cost effectiveness of peginterferon alfa plus ribavirin in this appraisal, but stated that analyses in future appraisals of treatments for hepatitis C should include sensitivity analyses accounting for the possibility of a spontaneous cure without treatment.

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 unless liver damage was present.

- 4.3.18 The Committee considered the disutilities associated with adverse reactions of treatment with peginterferon alfa plus ribavirin. It noted that none of the models included disutility associated with growth impairment. The Committee pointed out that such disutilities were included in the Assessment Group's economic model for [Human growth hormone \(somatropin\) for the treatment of growth failure in children \(review\)](#) (NICE technology appraisal 188), but that the children in that appraisal were considerably shorter than the average child with chronic hepatitis C. Nonetheless, the Committee would have expected the model to have included a utility decrement for growth impairment, considering that it is a significant adverse effect of peginterferon alfa plus ribavirin treatment. The Committee concluded, however, that, other than for extremely short children, this was unlikely to outweigh the benefits of treatment.
- 4.3.19 The Committee considered the use of peginterferon alfa plus ribavirin in children and young people with chronic hepatitis C who are co-infected with HIV. It concluded that, although these patients were not represented in the pivotal clinical trials, based on the current evidence available, there was no reason to make any different provision for them. It did, however, note that there might be occasions when ribavirin might interact with drugs for HIV, necessitating a review of the patient's optimal treatment strategy.
- 4.3.20 The Committee considered whether there were any benefits that were not adequately captured in the QALY calculation. It acknowledged that there were some health benefits gained by parents or carers as a result of children or young people receiving peginterferon alfa plus ribavirin treatment for chronic hepatitis C.

For these benefits to be given special consideration, the Committee acknowledged that they must provide more health benefits than treatments for other conditions. In this case, the clinical specialists and patient experts suggested that successful treatment might, in part, alleviate a mother's burden of psychological guilt of mother-to-child transmission of hepatitis C. Additionally, although the risk of non-maternal transmission is minimal, foster parents may be reluctant to foster children with hepatitis C and may be concerned about transmission to other children in the household, a concern that would be removed if a sustained virological response was achieved through treatment. Furthermore, the Committee acknowledged the significant public health impact of successful treatment on reducing HCV transmission rates to uninfected people in the UK population and considered that, if this benefit was included in the model, the results were likely to be even more favourable. The Committee agreed that there were health benefits that had not been adequately captured in the QALY calculation but that, because of the favourable cost-effectiveness results, this did not need any further action.

- 4.3.21 The Committee noted that the estimates of clinical effectiveness were key drivers of the differences in costs and outcomes in the cost-effectiveness analysis of peginterferon alfa-2a compared with peginterferon alfa-2b. However, because the clinical effectiveness estimates were very similar for both peginterferon alfa-2a and peginterferon alfa-2b (see section 4.3.2), the Committee was not convinced that there was sufficient evidence to recommend 1 treatment over the other. The Committee agreed that peginterferon alfa (2a and 2b) plus ribavirin were more effective and less costly than best supportive care across all genotypes, and it was certain that addressing the shortcomings identified in the economic evaluations presented would not alter its conclusion.

The technology		
Proposed benefits of the technology	Treatment with peginterferon alfa could provide a sustained virological response that could potentially last for the lifetime of the child or young person, effectively providing a cure.	4.3.7
	Treatment with peginterferon alfa could provide benefits to parents and carers, including reducing the guilt burden associated with maternal transmission of hepatitis C.	4.3.20
	Treatment with peginterferon alfa in young children could help avoid the social stigma associated with hepatitis C infection.	4.3.10
	The Committee concluded that, although peginterferon alfa plus ribavirin represented a useful treatment option for children with hepatitis C, the technologies themselves were not innovative for the purpose of this evaluation.	4.3.11
How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?		
What is the position of the treatment in the pathway of care for the condition?	Peginterferon alfa-2a and peginterferon alfa-2b are clinically equivalent and the decision to treat with either will largely be determined by clinical judgement and the specifics of the marketing authorisation.	4.3.2
	Children and young people are only treated once with peginterferon alfa plus ribavirin in UK clinical practice.	4.3.8
Adverse reactions	The main adverse reactions are: severe psychiatric and central nervous system effects, particularly depression, suicidal ideation and attempted suicide, weight loss and growth inhibition. The Committee concluded that peginterferon alfa has an impact on children's growth, but the problem of progressive liver disease outweighs the problems associated with being shorter than a child would otherwise have been without treatment.	4.3.9
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	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.	4.3.4

Relevance to general clinical practice in the NHS	The Committee heard 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.	4.3.5
Uncertainties generated by the evidence	Because the evidence base largely comprised single-arm studies that did not have any control groups receiving no therapy, the Committee would have expected the manufacturers' and Assessment Group's submissions to have provided supporting data from adult trials to establish the efficacy of peginterferon alfa (2a and 2b) plus ribavirin.	4.3.4
	Studies were presented to support the contention that children are 'cured' following peginterferon alfa plus ribavirin treatment. The studies that followed children with sustained virological responses 5 years on showed that the children remained healthy, but these studies were small and not necessarily representative of the UK population. The Committee would have expected data from trials in adults to be presented in order to augment the evidence of the likelihood of an enduring response from peginterferon alfa plus ribavirin in children.	4.3.7
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	Experience suggests that early treatment with peginterferon alfa plus ribavirin is better than later treatment, but the decision about whether and when to treat should be made by parents or carers together with the child or young person's clinician.	4.3.6
Estimate of the size of the clinical effectiveness including strength of supporting evidence	Peginterferon alfa (2a and 2b) plus ribavirin is an effective therapy in children and young people with chronic hepatitis C across all genotypes.	4.3.4
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee considered the Assessment Group's and the 2 manufacturer's economic models.	4.3.12

<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The Committee questioned the manufacturers' decision to rely on previous utility values without validating them and the Assessment Group's decision for using Swedish and Canadian health-related quality-of-life data, considering the Committee's preference for utility values derived from UK population studies.</p> <p>The Committee noted that none of the models included disutility associated with growth impairment.</p> <p>Although each of the models presented incorporated different stopping rules, the Committee would have expected the stopping rules to be consistent with clinical practice and the marketing authorisation of both products.</p> <p>Spontaneous sustained virological response without treatment was not included in MSD's or the Assessment Group's base-case, although they considered it in sensitivity analyses.</p> <p>Nevertheless, the Committee was certain that addressing the shortcomings identified in the economic evaluations would not alter its conclusion.</p>	<p>4.3.15</p> <p>4.3.18</p> <p>4.3.13</p> <p>4.3.16</p> <p>4.3.21</p>
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>Utility values used in the manufacturers' models were based on previous technology appraisals in adults and the values had not been updated, revalidated or presented to the Committee.</p> <p>Successful treatment could reduce HCV transmission rates to uninfected people in the UK population and if this benefit was included in the model, the results would likely be even more favourable.</p> <p>Treatment with peginterferon alfa plus ribavirin might, in part, alleviate a mother's burden of psychological guilt of mother-to-child transmission of hepatitis C and remove concerns about horizontal transmission.</p>	<p>4.3.15</p> <p>4.3.20</p> <p>4.3.20</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>N/A</p>	

What are the key drivers of cost effectiveness?	For the comparison of peginterferon alfa-2a with peginterferon alfa-2b, the key drivers of cost effectiveness were the estimates of clinical effectiveness.	4.3.21
Most likely cost-effectiveness estimate (given as an ICER)	The manufacturer's and Assessment Group's base-case results showed that peginterferon alfa-2a and peginterferon alfa-2b (both plus ribavirin) dominated best supportive care in all genotypes, except Roche's cost-effectiveness results for children and young people with HCV genotype 1, 4 or 5, which resulted in an ICER of £3900 per QALY gained.	4.3.12
Additional factors taken into account		
Patient access schemes (PPRS)	N/A	-
End-of-life considerations	N/A	-
Equalities considerations and social value judgements	During the scoping consultation, it was suggested that young people who misuse drugs, recent immigrants and asylum seeker who are children should be considered in this appraisal. However, because NICE does not exclude any specific groups of children and young people in this appraisal, this suggestion did not need further action.	-

5 Implementation

5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph

above. This means that, if a patient has chronic hepatitis C and the doctor responsible for their care think that peginterferon alfa and ribavirin are the right treatments, they should be available for use, in line with NICE's recommendations.

5.3 NICE has developed tools [[link to www.nice.org.uk/guidance/TAXXX](#)] to help organisations put this guidance into practice (listed below). [[NICE to amend list as needed at time of publication](#)]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Details are correct at the time of publication. Further information is available on the [NICE website](#).

Published

- [Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection](#). NICE public health guidance 43 (2012).
- [Boceprevir for the treatment of genotype 1 chronic hepatitis C](#). NICE technology appraisal guidance 253 (2012).
- [Telaprevir for the treatment of genotype 1 chronic hepatitis C](#). NICE technology appraisal guidance 252 (2012).
- [Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C \(part review of NICE technology appraisal guidance 75 and 106\)](#). NICE technology appraisal guidance 200 (2010).

- [Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C \(extension of technology appraisal guidance 75\)](#). NICE technology appraisal guidance 106 (2006).
- [Interferon alfa \(pegylated and non-pegylated\) and ribavirin for the treatment of chronic hepatitis C \(review and extension of technology appraisal guidance 14\)](#). NICE technology appraisal guidance 75 (2004).

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Hepatitis C. NICE clinical guideline. Publication date to be confirmed.

NICE Pathways

- [Hepatitis B and C testing](#). NICE Pathway (2012).

7 Review of guidance

- 7.1 The guidance on this technology will be considered for review by the Guidance Executive in September 2016. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler

Chair, Appraisal Committee

November 2013

8 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Amanda Adler (Chair)

Consultant Physician, Addenbrooke's Hospital

Dr Ray Armstrong

Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson

Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Professor John Cairns

Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine

Professor Peter Crome

Consultant Geriatrician and Professor of Geriatric Medicine

Dr Neil Iosson

General Practitioner

Anne Joshua

Associate Director of Pharmacy, NHS Direct

Dr Rebecca Kearney

Clinical Lecturer, University of Warwick

Terence Lewis

Lay Member

Dr Miriam McCarthy

Consultant, Public Health, Public Health Agency

Dr Elizabeth Murray

Reader in Primary Care, University College London

Professor Stephen Palmer

Professor of Health Economics, Centre for Health Economics, University of York

Dr Sanjeev Patel

Consultant Physician & Senior Lecturer in Rheumatology, St Helier University Hospital

Dr Danielle Preedy

Lay Member

Dr John Rodriguez

Assistant Director of Public Health, NHS Eastern and Coastal Kent

Alun Roebuck

Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust

National Institute for Health and Care Excellence

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Final appraisal determination – Peginterferon alfa and ribavirin for treating chronic hepatitis C in children and young people

Issue date: November 2013

Roderick Smith

Chief Finance Officer, Coastal West Sussex Clinical Commissioning Group

Cliff Snelling

Lay Member

Marta Soares

Research Fellow, Centre for Health Economics, University of York

Professor Andrew Stevens

Professor of Public Health, Department of Public Health and Epidemiology,
University of Birmingham

David Thomson

Lay Member

Dr Nicky Welton

Senior Lecturer in Biostatistics/Health Technology Assessment, University of
Bristol

Guideline representatives

The following person, observing the Committee meeting on behalf of the
Guideline Development Group, was invited to provide comments on this
document.

Dr Emmert Roberts

Research Fellow, National Clinical Guideline Centre, Royal College of
Physicians

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Richard Diaz

Technical Lead

Fiona Pearce

Technical Adviser

Jeremy Powell

Project Manager

9 Sources of evidence considered by the Committee

A. The assessment report for this appraisal was prepared by the Southampton Health Technology Assessments Centre:

- Hartwell D., Cooper K. et al, The clinical and cost-effectiveness of peginterferon alfa and ribavirin for the treatment of chronic hepatitis C in children and young people, January 2013

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I. Manufacturers/sponsors:

- Merck Sharp and Dohme
- Roche Products

II. Professional/specialist and patient/carer groups:

- British Liver Trust
- British Society of Gastroenterology
- Children's Liver Disease Foundation
- Hepatitis C Trust
- Royal College of Nursing
- Royal College of Paediatrics and Child Health
- Royal College of Pathologists
- Royal College of Physicians

III. Other consultees:

- Department of Health
- Welsh Government

IV. Commentator organisations (without the right of appeal):

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Medicines and Healthcare products Regulatory Agency

C. The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on peginterferon alfa and ribavirin by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Rosie Hague, clinical expert, Consultant in Paediatric Infectious Diseases and Immunology, nominated by Healthcare Improvement Scotland – clinical specialist
- Professor Deirdre Kelly, Professor of Paediatric Hepatology, nominated by Merck, Sharp and Dohme – clinical specialist
- Susan McRae, nominated by The Hepatitis Trust – patient expert

D. Representatives from the following manufacturers/sponsors attended the Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Merck Sharp and Dohme
- Roche Products