NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Overview

Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C in children and young people

This overview is a summary of:

- the evidence and views submitted by the manufacturers, the consultees and their nominated clinical specialists and patient experts and
- the assessment report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before comments on the assessment report have been received.

Key issues for consideration

Clinical effectiveness

- The Assessment Group review of the evidence on sustained virological response and other outcomes in children and adolescents is limited to 7 interventional studies of which 6 are single arm (uncontrolled) with 7 to 107 participants and 1 has a control group, but for which only one arm met the Assessment Group's inclusion criteria. The studies are therefore observational and the Assessment Group considered that the studies may not reflect the true effectiveness of the technologies. What is the Committee's view on the strength of the clinical evidence?
- What is the natural history of untreated disease, including attaining a sustained viral response?
- The studies were performed in different populations around the world, with different degrees of disease severity and genotype. Does the Committee consider that the populations in the studies reflect the paediatric population in the UK with chronic hepatitis C?

- What is the Committee's view on the adverse effect of treatment in relation to the potential benefits of the drugs?
- No studies directly compared peginterferon alfa-2a and peginterferon alfa-2b. What is the Committee's view on the reliability of the relative sustained virological response effect sizes of peginterferon alfa-2a and peginterferon alfa-2b from the single arm cohort studies? Is it appropriate to generalise from adults?
- Is it realistic to assume that trials would be performed using best supportive care as a comparison?

Cost effectiveness

- The Assessment Group's model used EQ-5D health-related quality of life data from 2 trials in adults from Sweden and Canada. In the absence of EQ-5D data in children, what is the Committee's view on the generalisability of these studies to children and adolescents with chronic hepatitis C in the UK?
- Does caring for a child or adolescent with chronic hepatitis C reduce the health-related quality of life of their parents and/or carers? Does this differ markedly from other diseases?
- Do children and adolescents experience stigma associated with having hepatitis C? If so, what is the Committee's view on the impact of stigma on the economic results presented?
- In the models presented by the Assessment Group, Merck Sharp and Dohme (MSD) and Roche Products, peginterferon alfa-2a and peginterferon alfa-2b cost less and were more effective than best supportive care. What is the Committee's view on using evidence from the adult population to populate the models?
- The Assessment Group and MSD compared the cost-effectiveness of peginterferon alfa-2a with peginterferon alfa-2b. In the Assessment Group's model peginterferon alfa-2a dominated peginterferon alfa-2b, except for those with genotype 2 or 3 where peginterferon alfa-2b dominated peginterferon alfa-2a, depending on the relative sustained

virological response of the treatments. By contrast, in the model presented by MSD peginterferon alfa-2b dominated peginterferon alfa-2a. What is the Committee's view on the relative cost-effectiveness of peginterferon alfa-2a and peginterferon alfa-2b for the overall population and by genotype?

1 Background: clinical need and practice

1.1 Hepatitis C is a disease of the liver caused by the hepatitis C virus (HCV). Serum HCV RNA (ribonucleic acid) indicates infection. There are 2 main phases of infection: acute and chronic. Acute hepatitis C refers to the period immediately after infection, while chronic hepatitis C is defined as infection that lasts for more than 6 months. People most commonly acquire the virus through percutaneous exposure to contaminated blood. In the UK the 2 major routes of transmission of HCV have been 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. Unlike hepatitis B, there is no vaccine for HCV.

1.2 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 with genotype 3a (prevalence 39%), and genotype 1a (prevalence 22%), occurring most commonly in people infected with HCV. Viral genotype predicts the effectiveness of anti-viral treatment; people infected with genotypes 2 and 3 generally respond better than those with genotypes 1, 4, 5 and 6.

1.3 Infection with HCV can lead to further complications including hepatic dysfunction, hepatic cirrhosis, hepatocellular carcinoma, and death. Progression to severe hepatitis or cirrhosis during childhood is rare (<5%) and the mean time to development of cirrhosis in people infected as infants is estimated at 28 years.

1.4 Estimates from the Health Protection Agency in 2011 indicate that 26 people aged 1 year or less and 21 people between the ages of 1 and 14 years were newly diagnosed with HCV in England in 2010. Estimates for chronic infection in children and young people are not available. A 2006 Scottish Medicine Consortium report on peginterferon alfa-2b estimated an initial population of 110 HCV-infected children with 30 new diagnoses being reported annually in Scotland.

1.5 The aim of treatment is to clear virus from the blood. Sustained virological response, which is defined as undetectable serum HCV RNA (ribonucleic acid) 6 months after the end of treatment, usually indicates resolution of infection, although relapse occurs in approximately 5% of people after 5 years. Whereas some adults with HCV receive protease inhibitors, children and young people who are HCV RNA positive with moderate or severe liver disease are currently considered for treatment with pegylated interferon and ribavirin.

2 The technologies

2.1 Peginterferon alfa-2a (Pegasys, Roche Products) in combination with ribavirin has a UK marketing authorisation to treat children and adolescents aged 5 and older with chronic hepatitis C, who test positive for serum HCV-RNA and who have not been previously treated. It is administered subcutaneously once weekly. The dose of peginterferon alfa-2a depends on the body surface area of the child. It should not be used in children with a body surface area of less than 0.71 m^2 for whom there is no available data. The recommended duration of treatment is 24 (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 at weeks 4 and 24. Virological response by week 12, as defined as a 2 log viral load decrease or undetectable levels of

HCV RNA has been shown to be predictive for sustained virological response. If toxicities occur, the dose of 1 or both drugs can be reduced.

2.2 Peginterferon alfa-2b (ViraferonPeg, Merck Sharp and Dohme (MSD)) in combination with ribavirin has a UK marketing authorisation to treat children and adolescents aged 3 and older with chronic hepatitis C without hepatic decompensation, who test positive for serum HCV-RNA and who have not been previously treated. Dosing of peginterferon alfa-2b for children and adolescents is determined by body surface area and the recommended dose is 60 micrograms/m^2/week subcutaneously in combination with ribavirin. The recommended duration of treatment is 1 year for children with genotype 1 or 4. Treatment should be discontinued after 12 weeks if HCV-RNA has dropped < $2\log_{10}$ compared to pre-treatment or if HCV-RNA is detectable at week 24. For children with genotype 2 or 3, treatment is 24 weeks. If toxicities occur, the dose of 1 or both drugs can be reduced until the adverse reactions abate.

2.3 Ribavirin is manufactured by Roche Products (Copegus) and MSD (Rebetol). Each product is indicated for the treatment of chronic hepatitis C and must only be used as part of a combination regiment with peginterferon alfa or interferon alfa.The marketing authorisation for Copegus does not include specific recommendations for use in children. Copegus should only be administered in combination with the interferon products made by Roche Products (peginterferon alfa-2a). Rebetol (MSD) oral solution and 200mg hard capsules, has a UK marketing authorisation for children and adolescents aged 3 years and older in combination with peginterferon alfa-2a or peginterferon alfa-2b. The recommended dose of ribavirin in combination with peginterferon alfa is based on body weight, with an average dose of 15 mg/kg/day, divided in 2 doses.

2.4 Peginterferon alfa-2a and 2b are contraindicated for treatment of hepatitis C in children and adolescents with a history of severe psychiatric conditions. The summaries of product characteristics for peginterferon alfa-2a and 2b include the following adverse reactions for treatment in children and adolescents: 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 growth inhibition is reversible. It is recommended that whenever possible the child should be treated after the pubertal growth spurt. For full details of adverse effects and contraindications, see the summaries of product characteristics.

2.5 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 £1.3292 per microgram and 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 m^2, a 24-week course of peginterferon alfa-2a and ribavirin costs approximately £2600 (peginterferon alfa-2a) and between £740 and £1480 (ribavirin), while a 48-week course of treatment costs approximately £5200 (peginterferon alfa-2a) and between £1480 and £2960 (ribavirin). A 24-week course of peginterferon alfa-2b and ribavirin costs approximately £2600 (peginterferon alfa-2b) and between £1286 and £1610 (ribavirin), while a 48-week course of treatment costs approximately £5100 (peginterferon alfa-2b) and between £2571

and £3220 (ribavirin). Costs may vary in different settings because of negotiated procurement discounts.

Table 1 Summary description of technologies

Manufacturer	**Roche Products**			**Merck Sharp and Dohme**	
Non-proprietary names	**Peginterferon alfa-2a**		**Ribavirin**	**Peginterferon alfa-2b**	**Ribavirin**
Proprietary names	Pegasys		Copegus	ViraferonPeg	Rebetol
Route of administration	Subcutaneous injection		Oral (tablets)	Subcutaneous injection	Oral (capsules or oral solution)
Dose	Body surface area (m^2)	micro grams (weekly)	15 mg/kg daily	60 micrograms /m^2 once weekly	15 mg/kg daily
	0.71-0.74	65			
	0.75-1.08	90			
	1.09-1.51	135			
	>1.51	180			
Acquisition cost (BNF edition 65, April 2013)	Prefilled syringe or pen 135-microgram = £107.76 180-microgram prefilled syringe = £124.40		**Tablets** (200 mg) 42-tab pack = £92.50 112-tab pack = £246.65 168-tab pack = £369.98 (400 mg) 56-tab pack = £246.65 £2.20 per 200mg	Pre-filled pen, powder for reconstitution 50 microgram = £66.46 80 microgram = £106.34 100 microgram = £132.92 120 microgram = £159.51 150 microgram = £199.38	**Oral solution** (200mg/5mL; bubblegum flavoured for children) 100 ml = £67.08 £3.35 per 200mg **Capsules** (200 mg) 84-cap pack = £160.69 140-cap pack = £267.81 168-cap pack = £321.38 £1.91 per 200mg
Average length of a course of treatment	48 weeks for patients with HCV genotypes 1 or 4. 24 weeks for patients with HCV genotypes 2 or 3.				
Average cost per course of treatment	24 weeks: £2586 48 weeks: £5172		**(avg 32kg child)** 24 weeks: £740 48 weeks: £1480 **(avg 53kg adolescent)** 24 weeks: £1480 48 weeks: £2960	24 weeks: £2552 48 weeks £5104	**Oral solution (avg. 32kg child)** 24 weeks: £1610 48 weeks £3220 **Capsules (avg 53kg adolescent)** 24 weeks: £1286 48 weeks: £2571

3 Remit and decision problem

3.1 The remit from the Department of Health for this appraisal was to review the clinical and cost effectiveness of peginterferon alfa in combination with ribavirin within their licensed indications for the treatment chronic hepatitis C in children and young people.[1] The decision problem is shown in Table 2.

Table 2 Decision problem comparison

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Population	Children and young people aged 3 to 17 years with chronic hepatitis C. All groups will be considered, including: • People with HIV co-infection • People with all grades of severity of chronic hepatitis C (mild, moderate and severe) • People who are treatment naive or, if appropriate, who have not responded and/or relapsed to previous treatments.	
Intervention	• Peginterferon alfa-2a in combination with ribavirin • Peginterferon alfa-2b in combination with ribavirin	
Comparators	Supportive care, including treatment without any form of interferon therapy	Supportive care (including treatment without any form of interferon therapy), and the interventions compared with each other within their licensed indications.
Outcomes	• virological response to treatment • sustained virological response • biochemical response (e.g. ALT) • liver inflammation and fibrosis • mortality • adverse effects of treatment, including effects on growth • health-related quality of life.	• virological response to treatment (e.g. HCV RNA levels at treatment week 12 or at the end of treatment) • sustained virological response (HCV RNA levels 6 months after treatment cessation) • biochemical response (changes in alanine aminotransferase levels) • liver inflammation and fibrosis • mortality • adverse effects of treatment including growth • health-related quality of life.

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[1] The original remit for this appraisal is to appraise the clinical and cost effectiveness of interferon alfa (pegylated and non-pegylated) and ribavirin in their licensed indications for the treatment and management of chronic hepatitis C.

Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	The Assessment Group uses a time horizon of 70 years, as this was considered long enough to capture all relevant costs and benefits, and a cycle length of 1 year.

4 Clinical-effectiveness evidence

4.1 The Assessment Group focused on 6 specific questions to determine the following: virological response to treatment; sustained virological response to treatment; biochemical response to treatment; histological response to treatment; change in quality of life; and adverse effects of treatment including effects on growth.

4.2 The Assessment Group identified 1 randomised controlled trial and 1 single-arm trial evaluating peginterferon alfa-2a and ribavirin. The randomised controlled trial was the pivotal regulatory trial (PEDS-C, Schwarz et al.) for treatment in people aged 5-18 years. Because the comparator arm was peginterferon monotherapy it did not meet the inclusion criteria for the appraisal. The Assessment Group used data from the intervention arm (n = 55) treating it as an uncontrolled observational study. The single-arm trial evaluating peginterferon alfa-2a and ribavirin (Sokal et al, n = 65) included children aged 6-17 years.

4.3 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., n = 107) included

children aged 3-17 years. The other four peginterferon alfa-2b studies included populations that were narrower than those specified in the UK marketing authorisation (Al Ali et al., single armed trial [n = 12, children aged 14-17], Ghaffar et al. [n = 7, children aged 8-16], Jara et al. [n = 30, children aged 3-16], Pawlowska et al. [n = 53, children aged 8-17]). No studies were identified in children and young people with HIV co-infection. The duration of the trials in the Asessment Group's efficacy review ranged from 24 to 52 weeks. Further characteristics of the trials are shown in Table 3.

Table 3 Characteristics of included studies

Study (n)	**Duration (weeks)**	**Age ranges (median)**	**HCV Genotype**	**HCV RNA / Fibrosis**
Peginterferon alfa 2-a and ribavirin				
PEDS-C Trial Schwarz 2011 + related publications (n = 55 single arm) multicentre / USA	48 Follow-up 24 post treatment	5-18 years (mean age 10.7)	Genotype 1: 45 (82%) Genotype 2: 4 (7%) Genotype 3: 6 (11%) Genotype 6: 0	≥ 600,000 IU/ml: 32 (58%) Mean HCV RNA: ~1,585,000 IU/ml No fibrosis: 7 (13%) Portal-periportal (Ishak 1-2): 43 (80%) Bridging (Ishak 3-4): 4 (7%) Cirrhosis (Ishak 5-6): 0
Sokal 2010 (n = 65) multicentre / Belgium, UK, Sweden, Brazil, Latvia	24 or 48 (according to genotype) Follow-up 24 weeks post treatment	6-17 years (mean age 11.3 for genotype 1 group and 12.6 for genotype 3)	Genotype 1: 45 (69%) Genotype 2: 2 (3%) Genotype 3: 16 (25%) Genotype 4: 1 (2%) Genotype 5 or 6: 1 (2%)	<500,000 IU/ml: 23 (36%) >500,000 IU/ml: 42 (65%) No fibrosis: 34 (52%) Grade F1: 21 (32) Grade F2: 9 (14)
Peginterferon alfa 2-b and ribavirin				
Al Ali et al., 2010 (n = 12) single centre / Kuwait	48 Follow-up 24 post treatment	14-17 years (mean age 15.75 years)	Genotype 4: 100%	Mean HCV RNA: 780,000 IU/ml (range 230,000 -1,800,000 IU/ml) Mean METAVIR fibrosis score: 0.67 (range 0-3)
Pawlowska et al., 2010 + abstract (n = 53) single centre / Poland	48 weeks (also states 24 or 48 according to genotype) Follow up at 24 weeks post treatment	8-17 years (mean age 13.6 years)	Genotype 1: 27 (50%) Genotype 3: 2 (4%) Genotype 4: 24 (46%)	<500,000 IU/ml: 21 (40%) >500,000 IU/ml: 29 (55%) Mean HCV RNA: 456,000 IU/ml Fibrosis score (modified Scheuer scale) ≤ stage 2: 100%

Study (n)	Duration (weeks)	Age ranges (median)	HCV Genotype	HCV RNA / Fibrosis
Wirth et al., 2010 + abstract (n = 107) multicentre / Austria, France, Germany, Italy, Spain, Argentina, Chile, USA, Puerto Rico	24 or 48 (according to genotype and viral load) Follow up at 24 weeks post treatment	3-17 years (mean age 10 years)	Genotype 1: 72 (67%) Genotype 2: 15 (14%) Genotype 3: 15 (14%) Genotype 4: 5 (5%)	<600,000 IU/ml: 58 (54%) >600,000 IU/ml: 45 (42%) Mean HCV RNA: 442,748 IU/ml METAVIR fibrosis score F0: 13 (12.5%); F1: 88 (82.2%); F2: 2 (1.9%); F3: 1 (1%)
Ghaffar et al., 2009 (n = 7) single centre / Egypt	52 Follow-up at 52 weeks post treatment	8-16 years (mean age not reported)	Genotype 4a: 1 (14%) Genotype 4b: 5 (71%) Unknown (not tested): 1 (14%)	Median HCV RNA: 145,000 IU/ml (range: 74,000 – 758,000 IU/ml) Fibrosis score not reported for all children and adolescents in the study
Jara et al, 2008 (n = 30) single centre / Spain	24 or 48 (according to genotype)	3-16 years (mean age 10 years)	Genotype 1: 26 (87%) Genotype 3: 3 (10%) Genotype 4: 1 (3%)	Mean HCV RNA: 100,000 IU/ml (range 100-1,000,000 IU/ml) Knodell fibrosis score <4: 58%; 4-7: 31%; ≥ 8: 10%

4.4 Concentrations of HCV RNA virus (viral load) at baseline varied across the 7 included studies. In the 2 peginterferon alfa-2a studies, approximately 60% of participants had high viral loads (> 500,000 IU/ml or ≥ 600,000 IU/ml), and 1 study of peginterferon alfa-2b also reported a high baseline viral load with a mean of 780,000 IU/ml. Two other peginterferon alfa-2b studies reported similar proportions of children and adolescents with either high (> 500,000 or 600,000 IU/ml) or low (< 500,000 or 600,000 IU/ml) HCV RNA levels. In the study by Ghaffar et al. (peginterferon alfa-2b) most of the children and adolescents had low HCV RNA viral load levels at baseline (median 145,000 IU/ml). The Jara et al. study (peginterferon alfa-2b) reported a mean HCV RNA viral load level of 100,000 IU/ml. The Assessment Group cautioned that according to clinical opinion, there is generally no single agreed definition of what constitutes a ‘high’ or ‘low’ HCV viral load level. Levels of fibrosis indicated mild liver disease in most or all of the

population across the 7 studies, but it was not reported in Ghaffar et al.

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

Efficacy results

4.6 The measure of effectiveness taken from the uncontrolled trials reflected the proportion of participants who received treatment, and achieved a virological response.

Sustained virological response

4.7 The 7 studies reported sustained virological response as the primary outcome. Sustained virological response was defined as undetectable serum HCV RNA at 24 weeks after the end of treatment in both peginterferon alfa-2a studies and 4 peginterferon alfa-2b studies and 12 months after the end of the Ghaffar et al. study (peginterferon alfa-2b). The proportions of children receiving peginterferon alfa-2a or -2b and ribavirin achieving a sustained virological response are summarised in Table 4.

Table 4 Sustained virological response

Study	Treatment	n	Sustained Virological Response %
Schwarz et al.	Peginterferon alfa-2a and ribavirin 48 weeks	55	53%, 95% CI 40-66% (29/55)
Sokal et al.	Peginterferon alfa-2a and ribavirin 24 or 48 weeks	65	66%, (43/65)* (2 ND)**
Al Ali et al.	Peginterferon alfa-2b and ribavirin 48 weeks	12	75% (9/12)
Pawlowska et al.	Peginterferon alfa-2b and ribavirin	53	49% (26/53)

	24 or 48 weeks		
Wirth et al.	Peginterferon alfa-2b and ribavirin 24 or 48 weeks	107	65% (70/107)
Ghaffar et al.	Peginterferon alfa-2b and ribavirin 52 weeks	7	29% (2/7)
Jara et al.	Peginterferon alfa-2b and ribavirin† 24 or 48 weeks	30	50% (15/30)
* As calculated by the Assessment Group. ** ND not defined by authors but assumed by Assessment Group to mean 'not determined' † A lower dose of peginterferon alfa-2b was used compared to other studies (1.0 microgram/kg/week compared with 1.5 microgram/kg/week) CI, confidence interval			

4.8 In both studies evaluating peginterferon alfa-2a sustained virological responses were similar, with 53% in the Schwarz et al. study and 66% in the Sokal et al. study. All of the participants in the Schwarz et al. study who achieved a sustained virological response showed a durable response 2 years later. For peginterferon alfa-2b sustained virological response to treatment ranged from 29% to 75%, although the Assessment Group commented that the 2 studies reporting the highest and lowest rates were very small. The rates of sustained virological response in the other 3 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]). It should be noted that the Jara et al. study used a lower dose of peginterferon alfa-2b (1.0 microgram/kg per week) compared with the other peginterferon alfa-2b studies (1.5 microgram/kg per week). The Assessment Group commented that it was unclear what impact, if any, this had on the rate of sustained virological response achieved in the trial.

Sustained virological response according to genotype

4.9 Both peginterferon alfa-2a studies (Schwarz et al. and Sokal et al.) and 3 of the peginterferon alfa-2b studies (Pawlowska et al., Wirth et al. and Jara et al.) reported sustained virological response rates according to HCV genotype. Table 5 shows the results. Response

rates across the 2 studies evaluating peginterferon alfa-2a showed that participants with genotype 2 or 3 had a higher response rate than participants with other genotypes (80% to 89% compared with 47% to 57%). In studies evaluating peginterferon alfa-2b, response rates were similar for genotype 1, ranging from 46% to 53%, while response rates for genotype 2 or 3 and genotype 4 were more variable (50% to 100% and 0 to 80%, respectively).

Table 5 Sustained virological response according to genotype

Study	Treatment	Genotype	Sustained virological response % (n/N)
Schwarz et al. (PEDS-C)	Peginterferon alfa-2a and ribavirin 48 weeks, n=55	Genotype 1	47%, 95% CI 32-61% (21/45)
		Genotype 2-6*	80%, 95% CI 55-100% (8/10)
Sokal et al.	Peginterferon alfa-2a and ribavirin 24 or 48 weeks, n=65	Genotype 1, 4, 5 or 6†	57% (27/47) (1 ND)††
		Genotype 2 or 3	89% (16/18) (1 ND)††
Pawlowska et al.	Peginterferon alfa-2b and ribavirin 24 or 48 weeks, n=53	Genotype 1	48% (13/27)
		Genotype 3	50% (1/2)
		Genotype 4	50% (12/24)
Wirth et al.	Peginterferon alfa-2b and ribavirin 24 or 48 weeks, n=107	Genotype 1	53% (13/72)
		Genotype 2 or 3	93% (28/30)
		Genotype 4	80% (4/5)
Jara et al.	Peginterferon alfa-2b and ribavirin† 24 or 48 weeks, n=30	Genotype 1	46% (12/26)
		Genotype 3	100% (3/3)
		Genotype 4	0% (0/1)

* No children or adolescents with genotype 4, 5 or 6 were included in the study.

† Two out of 65 children and adolescents in this grouping were found to have genotype 4, 5 or 6 HCV. The remaining were children and adolescents with genotype 1 HCV.

†† ND not defined by authors but assumed by Assessment Group to mean 'not determined'

CI, confidence interval

Sustained virological response according to viral load at baseline

4.10 Both peginterferon alfa-2a studies (Schwarz et al. and Sokal et al.) and 1 peginterferon alfa-2b study (Wirth et al.) reported sustained virological response rates according to baseline viral load, stratified into low (<500,000 or ≤600,000 IU/ml) or high (>500,000 or ≥600,000 IU/ml) HCV RNA viral load (Table 6).

Table 6 Sustained virological response according to viral load at baseline

Study	Treatment	HCV RNA viral load	Sustained virological response % (n/N)
Schwarz et al. (PEDS-C)	Peginterferon alfa-2a and ribavirin 48 weeks, n=55	less than 600,00 IU/ml	70% (16/23)
		greater than or equal to 600,000 IU/ml	50% (16/32)
Sokal et al.	Peginterferon alfa-2a and ribavirin 24 or 48 weeks, n=65	less than 500,00 IU/ml Genotype 1, 4, 5 or 6 Genotype 2 or 3	74% (17/23) 62% (8/13) 90% (9/10)
		greater than 500,000 IU/ml Genotype 1, 4, 5 or 6 Genotype 2 or 3	55% (22/40) 45% (15/33) 100% (7/7)
Wirth et al.	Peginterferon alfa-2b and ribavirin 24 or 48 weeks, n=107	less than or equal to 600,000 IU/ml Genotype 1 Genotype 2 or 3 Genotype 4	79% (46/58)* 72% (28/39) 94% (15/16) 100% (3/3)
		greater than 600,000 IU/ml Genotype 1 Genotype 2 or 3 Genotype 4	49% (22/45)* 29% (9/31) 100% (13/13) 0% (0/1)
* Total calculated by Assessment Group.			

4.11 The results suggest that children and adolescents with a low baseline viral load appear to achieve higher sustained virological response rates (range 70-79%) than those with a higher load (range 49-55%). Sokal et al. and Wirth et al. reported that a greater proportion of children with genotype 2 or 3 achieved a sustained virological response compared to those with genotype 1, 4, 5 or 6 regardless of viral load. Wirth et al. reported that in people with genotype 1, the rate of sustained virological response was higher in those with low baseline viral load than in those with high baseline viral load (72% compared with compared with 29%, p=0.0006).

Sustained virological response according to previous treatment

4.12 The 2 peginterferon alfa-2a studies only included children who were treatment-naïve. Two peginterferon alfa-2b studies included both treatment-naïve and previously treated children. Pawlowska et al. reported that 45% of the children and adolescents (24 out of 54)

had been previously treated with non-pegylated interferon alfa-2b with ribavirin for 52 weeks, 2 to 5 years earlier. Jara et al. reported that 20% of the children and adolescents in the study had been previously treated with non-pegylated interferon monotherapy 3 to 5 years earlier. Table 7 displays the results.

Table 7 Sustained virological response according to previous treatment

Study	Treatment	Sustained virological response according to previous treatment	
		Treatment history	**Sustained virological response % (n/N)**
Pawlowska et al.	Peginterferon alfa-2b + ribavirin 24 or 48 weeks, n=53	Treatment naïve	62% (18/29)*
		Genotype 1	62% (10/16)
		Genotype 3	50% (1/2)
		Genotype 4	72% (8/11)
		Previously treated	33% (8/24)*
		Genotype 1	27% (3/11)
		Genotype 3	n/a**
		Genotype 4	30% (4/13)
Jara et al.	Peginterferon alfa-2b + ribavirin 24 or 48 weeks, n=30	Treatment naïve	55% (11/20)
		Previously treated	17% (1/6)†

* Numerators in the genotype subgroups (as reported in the publication) do not add up correctly to the total number of treatment naïve and previously treated participants.

** No previously treated patients had genotype 3.

† Of 30 patients, 26 were included, all genotype 1; remaining 4 patients (3 x genotype 3, 1 x genotype 4, all treatment naïve) were not included.

4.13 Generally, rates of sustained virological response were higher in children and adolescents who were treatment-naïve in both studies (55-62%) compared to those who had been previously treated (17-33%). The Assessment Group commented that numerators in the genotype subgroups did not add up correctly to the total number of treatment-naïve and previously treated children and adolescents, and that the numbers of children and adolescents in these subgroups were small.

Sustained virological response according to baseline alanine aminotransferase levels

4.14 Three studies reported sustained virological response rates according to hepatic dysfunction measured by concentrations of

alanine aminotransferase in serum at baseline. However, the Assessment Group found that none of the studies defined what should constitute normal ranges. Results are shown in Table 8.

Table 8 Sustained virological response according to baseline alanine aminotransferase concentrations

Study	Treatment	Sustained virological response according to alanine aminotransferase levels	
		Alanine aminotransferase concentrations (ALT)	**Sustained virological response % (n/N)**
Schwarz et al. (PEDS–C)	Peginterferon alfa-2a + ribavirin 48 weeks, n=55	Normal ALT	70%, 95% CI 51-88% (16/23)
		ALT > Upper normal limit	41%, 95% CI 24-58% (13/32)
Sokal et al.	Peginterferon alfa-2a + ribavirin 24 or 48 weeks, n=65	Normal ALT	80% (24/30)
		Genotype 2 or 3	89% (8/9)
		Genotype 1, 4, 5 or 6	89% (17/19)
		Abnormal ALT*	58% (19/33)
		Genotype 2 or 3	100% (8/8)
		Genotype 1, 4, 5 or 6	37%** (10/27)
Wirth et al.	Peginterferon alfa-2b + ribavirin 24 or 48 weeks, n=107	Normal ALT	67% (42/63)†
		Genotype 1	56% (23/41)
		Genotype 2 or 3	90% (18/20)
		Genotype 4	50% (1/2)
		Abnormal ALT*	64% (28/44) †
		Genotype 1	48% (15/31)
		Genotype 2 or 3	100% (10/10)
		Genotype 4	100% (3/3)

* Not defined.
** Data are from a table in the publication; also states 36% in the publication text.
† Calculated by Assessment Group.

4.15 In the 2 peginterferon alfa-2a studies, the rate of sustained virological response was higher in those with normal alanine aminotransferase levels at baseline (range 70-80%) compared with those whose baseline alanine aminotransferase levels were abnormal (range 41-58%). Sokal et al. showed that in children and adolescents with normal baseline alanine aminotransferase concentrations, sustained virological response rates did not differ by genotype. However, for children with abnormal baseline alanine aminotransferase concentrations, those with genotype 2 or 3 had a higher sustained virological response rate than other genotypes,

although most (81.8%) had HCV genotype 1. In the 2 peginterferon alfa-2b studies sustained virological response was similar across levels of alanine aminotransferase concentrations at baseline (67% and 64% respectively).

Sustained virological response according to liver histology

4.16 Both peginterferon alfa-2a studies reported sustained virological response according to baseline liver histology. Schwarz et al. reported stage of fibrosis (none or stage 1-6) using the Ishak fibrosis classification system, as well as inflammation (minimal, grade 1-3 or mild-marked, grade 4-12) using the Knodell histological activity index. Sokal et al. reported sustained virological responses according to the presence of absence of fibrosis but did not specify a fibrosis classification system, which prevented the Assessment Group from making any comparisons. None of the peginterferon alfa-2b studies reported sustained virological response according to liver histology.

Table 9 Sustained virological response according to liver histology

Study	Treatment	Sustained virological response according to liver histology	
		Histological parameter	**Sustained virological response % (n/N)**
Schwarz et al. (PEDS-C)	peginterferon alfa-2a+ ribavirin 48 weeks, n=55	Fibrosis stage	
		None	43%, 95% CI 6-80% (3/7)
		Stage 1-6	53%, 95% CI 39-67% (25/47)
		Inflammation histological activity index	
		Minimal (1-3)	43%, 95% CI 23-64% (10/23)
		Mild-Marked (4-12)	58%, 95% CI 41-75% (18/31)
Sokal et al.	peginterferon alfa-2a+ ribavirin 24 or 48 weeks, n=65	No fibrosis	76% (25/33)
		Genotype 2,3	100% (8/8)
		Genotype 1,4,5,6	68% (17/25)
		Fibrosis	60% (18/30)
		Genotype 2,3	89% (8/9)
		Genotype 1,4,5,6	48% (10/21)

4.17 Of children without hepatic fibrosis at baseline 43% (Schwarz et al. study) compared with 76% (Sokal et al. study) had sustained virological response rates, although the Assessment Group noted the limited numbers in the Schwarz et al. subgroup (n = 7). Sustained virological response rates in children with some degree of fibrosis were 53% (Schwarz et al) and 60% (Sokal et al.).

Non-response and relapse

4.18 The proportion of children and adolescents whose HCV did not respond to treatment was reported in the 2 peginterferon alfa-2a studies (12% in Sokal et al.; 25% in Schwarz et al.) and 3 of the peginterferon alfa-2b studies (17% in Al Ali et al., 51% in Pawlowska et al. and 47% in Jara et al.) . The Assessment Group noted that none of the studies provided a specific definition of non-response to treatment.

4.19 HCV relapse rates for children and adolescents were reported by Schwarz et al. (17%) and 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] and 3% in Jara et al.). Three studies defined relapse as the reappearance of HCV RNA (detectable HCV RNA at week 72; Pawlowska et al.), at last follow-up (Wirth et al.), or after stopping therapy (Schwarz et al.) after previously having undetectable HCV RNA at the end of treatment. Two of the peginterferon alfa-2b studies reported data that the Assessment Group inferred to be HCV relapse (Al Ali et al. and Ghaffar et al.). Results are presented in Table 11.

Table 10 Non-response and relapse

Study	Treatment	Non-response % (n/N)	Relapse % (n/N)
Schwarz et al.	peginterferon alfa-2a+ ribavirin 48 weeks, n=55	25% (14/55)	17% (9/55)*
Sokal et al.	peginterferon alfa-2a+ ribavirin 24 or 48 weeks, n=65	12% (8/65) (NB: all participants with non-response had genotypes 1, 4, 5 or 6 only)	NR
Al Ali et al.	peginterferon alfa-2b + ribavirin	17% (2/12)	8% (1/12)

	48 weeks, n=12		
Pawlowska et al.	peginterferon alfa-2b + ribavirin 24 or 48 weeks, n=53	51% (27/53)	17% (9/53) (NB: reported as 7.5% for whole group in abstract but assumed to be an error)
Wirth et al.	peginterferon alfa-2b + ribavirin 24 or 48 weeks, n=107	NR	12% (9/72)** 8% (9/107)***
Jara et al.	peginterferon alfa-2b + ribavirin 24 or 48 weeks, n=30	47% (14/30)	3% (1/30)
NR not reported. * Calculated by Assessment Group ** Genotype 1 only calculated by Assessment Group *** Whole cohort calculated by Assessment Group			

Biochemical response

4.20 Biochemical response, defined as changes in liver enzyme concentrations in response to treatment, was recorded by 3 of the 5 peginterferon alfa-2b studies but neither of the peginterferon alfa-2a studies. In the study by Ghaffar et al., median concentrations of hepatic transaminases declined to approximately 50% of their baseline values after 52 weeks. Wirth et al. reported that normalisation of alanine aminotransferase occurred in 34 of 44 children and adolescents (77%) who had elevated alanine aminotransferase at baseline. Jara et al. reported that 28 of 30 children and adolescents (93%) had elevated alanine aminotransferase levels at baseline and that in14 of the 15 children (93%) who attained a sustained virological response during the first month, alanine aminotransferase concentrations returned to normal and remained normal at follow up. The Assessment Group commented that it was difficult to compare what would be considered ‘normal’ ranges in clinical practice to the ranges of hepatic transaminases concentrations found in these studies.

Histological response

4.21 Neither of the 2 studies on peginterferon alfa-2a reported histological outcomes. For peginterferon alfa-2b, Ghaffar et al. reported results for only 4 of the 7 children. Based on the

histological activity index, 3 children improved and 1 child's fibrosis regressed. The Assessment Group commented that the results should be interpreted with caution.

Growth and weight loss

4.22 Problems with growth and weight are listed in the summary of product characteristics as adverse effects of treatment. One study of peginterferon alfa-2a (Sokal et al.) and 3 of peginterferon alfa-2b (Pawlowska et al., Wirth et al. and Jara et al.) reported height and weight changes during treatment. . Sokal et al. reported that baseline and follow up Z-scores for height and weight showed little influence on growth rates (-0.4 ± 1.0 and -0.5 ± 1.1 and -0.3 ± 0.9 and -0.3 ± 1.0, respectively). Pawlowska et al. suggested 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 adolescents (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, but the participants did not regain their height percentile. Wirth et al. observed that 70% of children and adolescents (75/107) had an inhibited growth velocity to less than the 3rd percentile for age and sex during treatment. Mean growth velocity was 2.47 per year during treatment and 5.73 per year in the follow up period. Mean height percentiles were 50.87 in the treatment period and 44.25 at the end of follow up, with mean changes in the height percentile of -7.7 and 1.1 during the treatment and follow up periods respectively. The decrease in mean height percentile during treatment was greater in children and adolescents whose treatment duration was longer (n=55,

mean 334 days) than in those whose treatment duration was shorter (n=52, mean 155 days).

4.23 The 3 studies of peginterferon alfa-2b each reported that the participants lost weight during treatment. Jara et al. observed that 67% of children and adolescents (20/30) experienced weight loss, with 23% (7/30) losing more than 5% of their baseline weight. Weight gain occurred when treatment stopped. Pawlowska et al. observed that 43% of participants (23/53) experienced weight loss exceeding 10% of baseline weight, with the proportion being lower for children not previously treated (34.5%, 10/29) than for those previously treated (54.2%, 13/24). Wirth et al. reported that 19% of children and adolescents (20/107) lost weight, with a mean change in the weight percentile of -15.5 during treatment and 12.3 during follow up periods.

Adverse events – peginterferon alfa-2a

4.24 Few participants stopped therapy because of adverse events, (3% Sokal et al. to 7% Schwarz et al.). Approximately 23% (Sokal et al.) to 51% (Schwarz et al.) of participants modified their dosages. The most frequent events leading to dose modification were neutropaenia, which was reported in Sokal et al. with an incidence of 17%, and anaemia reported in Sokal et al. and Schwarz et al., with incidences of 5% and 11% respectively.

4.25 Serious adverse events were defined differently by both studies; Schwarz et al. reported a rate of 4% considered possibly secondary to the drug therapy. Sokal et al. reported a rate of 6% however it was unclear if the serious adverse events were related to the drug therapy. No deaths were reported in either study.

4.26 The most frequent adverse events reported by Sokal et al. and Schwarz et al. included flu-like symptoms, headache, injection site reactions, myalgia or arthralgia, irritability and fatigue. Schwarz et al. reported that gastrointestinal symptoms were relatively frequent

(56%) while Sokal et al. reported that 38% of participants reported abdominal pain. Schwarz et al. reported haematological adverse events which returned to baseline when treatment stopped, but haematological adverse events were not reported by Sokal et al., except for reasons of dose discontinuation or modification. The Assessment Group noted that because the trials were uncontrolled, it was not possible to test whether the adverse events were associated with treatment.

4.27 Whether duration of treatment was associated with adverse events was reported by Sokal et al in relation to disordered thyroid hormone which occurred in 15% of children and adolescents who were treated for 48 weeks and in none treated for 24 weeks.

Adverse events - peginterferon alfa-2b

4.28 The proportion of participants who had to stop treatment because of adverse events was reported by 2 studies and ranged from 1% (Wirth et al.) to 10% (Jara et al.). The proportion of participants who modified their dose for any adverse event ranged from 0% (Ghaffar et al.) to 25% (Wirth et al.) however this range was reinterpreted by the Assessment Group to 53%. Among specific adverse events, anaemia (0% - 33%) and neutropaenia (12%-23%) were the most frequent events that led to dose modification. Wirth et al. provided results for dose modification by age, showing that adolescents aged 12-17 years had a higher incidence of dose modification (35%) than children aged 3-11 years (19%).

4.29 None of the studies of peginterferon alfa-2b explicitly reported serious adverse events or deaths.

4.30 All the studies with peginterferon alfa-2b reported the incidence of specific adverse events. The most commonly-reported adverse events were (as for peginterferon alfa-2a) flu-like symptoms and/or fever, affecting 66% to 100% of children and adolescents in the

study. Other frequent adverse events reported were: headache (45%-67%), anaemia (11%-33%), leukopaenia (10%-67%), neutropaenia (17-33%), myalgia and/or arthralgia (33%-58%) abdominal pain (21%-43%), injection site reactions (29%-34%) and nausea and/or vomiting (27%-45%). The Assessment Group commented that all of the studies do not consistently report adverse events, which limits interpretation. The Assessment Group noted that because the trials were uncontrolled, it was not possible to test whether the adverse events were associated with treatment.

4.31 Differences in the incidence of adverse events by age were reported by Wirth et al. Some events occurred more frequently in people aged age 12 to 17 years than in those aged 3 to 11 years. These were blood and lymphatic disorders (30% compared with 9%), neutropaenia (23% compared with 6%) and anaemia (10% compared with 4%). No statistical tests were reported.

4.32 Differences in the incidence of adverse events between children previously-treated or not-treated were reported by Pawlowska et al. Adverse events that were more frequent in the previously-treated subgroup were flu-like symptoms (79% compared with 55%), headache (67% compared with 28%), weight loss greater than 10% (54% compared with 35%), local reaction at injections sites (50% compared with 21%), abdominal pain (42% compared with 3%) and neurasthenia (29% compared with 14%). In contrast, thrombocytopenia was more frequent in the treatment-naïve subgroup (21% compared with 8%). No statistical tests were reported.

Health-related quality of life

4.33 The PED-C trial (peginterferon alfa-2a; Schwarz et al.) reported changes in quality of life following 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 while the Children's Depression Inventory was completed by the child. Most of the children and adolescents (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 relative to baseline, indicating worse physical aspects of quality of life, with15% experiencing a clinically significant decline and no participants experiencing a clinically significant improvement ($p = 0.013$). After 1 or 2 years of follow up of all children who completed 48 weeks of treatment, no differences from baseline ($p > 0.05$) for any of the outcome measures were noted.

4.34 None of the 5 studies on peginterferon alfa-2b reported quality of life outcomes.

Assessment Group's critique of MSD's clinical effectiveness submission

4.35 MSD's submission reported a systematic review of clinical effectiveness which included 8 studies, but only presented study characteristics for 5. Of these 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. and Wirth et al.) and 2 for peginterferon alfa-2a (Schwarz et al. [PEDS-C] and Sokal et al.). Of the studies included in the manufacturer's submission but excluded from the Assessment Report, one had included participants older than the age range specified in the scope, and

the other because participants had previously received non-pegylated interferon. The Assessment Report included the Ghaffar et al. study not included in the MSD submission.

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

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

4.37 According to the Assessment Group, Roche did not conduct a systematic review of clinical effectiveness evidence and that Roche's bibliographic databases and search strategies were not sufficiently detailed to reproduce the evidence. Roche's clinical effectiveness section of the submission provided results primarily from Schwarz et al. (PEDS-C), Sokal et al. and 2 other uncontrolled trials which did not meet inclusion criteria for the decision problem because for one study the population was older than that specified in the scope and because the other study was retrospective without details of peginterferon dose or treatment duration. The Assessment Group commented that Roche did not report the methods it used for screening, data extraction and quality assessment.

4.38 The Assessment Group noted that Roche reported comparative data for both arms of the study by Schwarz et al. (PEDS-C), even though peginterferon alfa-2a monotherapy is outside the marketing authorisation and scope. The Assessment Group noted that the rates of 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, while effects of treatment on weight, height and growth were reported only from the studies excluded from the Assessment Group's evaluation.

4.39 The Assessment Group commented that the Roche submission appeared uncritical and did not interpret the clinical evidence. The Assessment Group also commented that although Roche stated in its submission that there is no safety concern with regard to adverse events resulting from peginterferon alfa-2a treatment, it reached this conclusion using data from the Schwarz et al study only in which both treatment arms received peginterferon alfa-2a.

5 Comments from other consultees

5.1 Comments were received from the Children's HIV Association, the Hepatitis C Trust and NHS East Riding of Yorkshire. One consultee commented that peginterferon alfa-2a and 2b should be recommended because they are as effective and well-tolerated in children as in adults. Another consultee commented that estimates of prevalence may underestimate the number of children and young people with HCV; if peginterferon alfa-2a and peginterferon alfa-2b in combination with ribavirin treatment were approved, referrals for treatment may be greater than anticipated.

5.2 One consultee commented that there is limited evidence on which to base treatment strategies in children with hepatitis C infection,

and even less evidence in those HIV/hepatitis co-infection. . The consultee called for a coordinated and rational strategy for delivering and investigating existing and new treatments.

6 Cost-effectiveness evidence

6.1 The Assessment Group carried out a systematic review to identify existing economic evaluations of peginterferon alfa-2a and peginterferon alfa-2b treatment in children with chronic hepatitis C. It identified 1 conference abstract andt one paper but neither study met its criteria for inclusion.

6.2 The Assessment Group also undertook a systematic review to identify information on the health-related quality of life of people with chronic hepatitis C. Its aim was to populate the economic model (with a lifetime horizon) with health state utility values to calculate quality-adjusted life years (QALYs). It restricted searches to studies using EQ-5D. The Assessment Group identified 2 published studies (Bjornsson et al. and Chong et al.) performed in adults, but no studies in children.

6.3 Bjornsson et al. evaluated health-related quality of life using the Short Form-36 (SF-36) and EQ-5D questionnaires in adults comparing participants with mild to moderate fibrosis with those with cirrhosis (Table 12). The study showed that EQ-5D was 0.656 and 0.811 for decompensated cirrhosis and mild to moderate fibrosis ($p < 0.001$). The value of EQ-5D in people with chronic hepatitis C and sustained virological response (0.819), was similar to that of healthy controls from the Swedish population.

Table 11 Health related quality of life utility results from Bjornsson et al.

Indication / disease	Chronic HCV	Compensated cirrhosis	Decompen-sated cirrhosis	Sustained virological response
Participants, n	158	76	53	52
Age, median (interquartile range)	46 (13)	52 (11)	55 (10)	51 (14)
Sex, %	M 62%; F 38%	M 76%, F 24%	M 71%, F 29%	M 56%, F44%
EQ-5D index value: mean (standard deviation)	0.811 (0.230)	0.749 (0.212)	0.656 (0.266)	0.792 (0.209)

6.4 Chong et al. evaluated the health-related quality of life of 193 people with chronic hepatitis C from Canada using EQ-5D and other measurements (Table 13). They observed that people with decompensated cirrhosis, hepatocellular carcinoma or liver transplant all had a lower health-related quality of life than the general Canadian population health-related quality of life norms (0.821, 95% CI 0.810 to 0.832) whereas people with a sustained virological response had similar values (0.83, 95% CI 0.77 to 0.90). A UK based study by Thompson Coon et al. applied UK social preference weights to individual patient data for compensated cirrhosis (0.74 [95% CI 0.66 to 0.83]), decompensated cirrhosis (0.66 [95% CI 0.46 to 0.86]) and hepatocellular carcinoma (0.64 [95% CI 0.44 to 0.86]) to produce EQ-5D values relevant to the UK population which resulted in utility values similar to those observed in Chong et al. (0.74 [95% CI 0.66 to 0.83], 0.66 [95% CI 0.46 to 0.86], 0.65 [95% CI 0.44 to 0.86], respectively).

Table 12 Health related quality of life utility results from Chong et al.

	No biopsy	Mild / moderate	Compen-sated cirrhosis	Decom-pensated cirrhosis	Hepato-cellular cancer	Transplant	Sustained virological response
Participants, n	35	44	24	9	15	30	36
Age, mean (SE)	47 (2.1)	44 (1.5)	57 (2.0)	57 (3.9)	63 (2.7)	54 (1.7)	48 (1.3)

Sex, %	M: 51 F: 49	M: 73 F: 27	M: 29 F: 71	M: 67 F: 33	M: 93 F: 7	M: 70 F: 30	M: 64 F: 36
Mean utility (95% CI)	0.73 (95% CI 0.62 to 0.83)	0.76 (95% CI 0.68 to 0.83)	0.74 (95% CI 0.66 to 0.83)	0.66 (95% CI 0.46 to 0.86)	0.65 (95% CI 0.44 to 0.86)	0.69 (95% CI 0.62 to 0.77)	0.83 (95% CI 0.77 to 0.90)
UK social preference weight applied mean utility, (Thompson Coon et al.)	-	-	0.75 (95% CI 0.66 to 0.83)	0.66 (95% CI 0.46 to 0.86)	0.64 (95% CI 0.44 to 0.86)	-	-
CI – Confidence intervals							

6.5 The Assessment Group observed that both studies assessed different stages of chronic hepatitis C and concluded that the estimates were sufficiently robust to use in its economic evaluation.

Roche's economic model for peginterferon alfa-2a in combination with ribavirin

6.6 Roche submitted an economic evaluation using a Markov model with a structure similar to other models used to evaluate technologies treating hepatitis C in adults. Roche compared the costs and health outcomes of treatment with peginterferon alfa-2a in combination with ribavirin with best supportive care (no treatment). Roche's model extrapolated the health effects of peginterferon alfa-2a in combination with ribavirin in children and adolescents with hepatitis C reflecting the population characteristics of the clinical trials over a 30-year time horizon. Children enter the model at age of 11 years in a model state of mild or moderate HCV-related fibrosis (88% and 12%, respectively) based on the weighted average of children and adolescents participating in the peginterferon alfa-2a studies. Regarding duration of treatment, children with HCV genotype 1, 4 or 5 whose disease has responded to treatment with peginterferon alfa-2a in combination with ribavirin at 24 weeks receive treatment for 48

weeks. Children with HCV genotype 2 and 3 were split into two groups to compare 24 week treatment with 48 week treatment. One group receives treatment for 24 weeks only and the other for 48 weeks (if their HCV has responded to treatment at 24 weeks). If treatment does not result in sustained virological response, children with HCV 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. Roche estimated transition probabilities from Guido et al, a multicentre retrospective study in children with chronic HCV. Roche used transition probabilities from adults used in previous appraisals for chronic HCV for transitions to decompensated cirrhosis, hepatocellular carcinoma and liver transplantation. 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 the general population. Roche assumed that the mortality risks for children in the decompensated cirrhosis, hepatocellular carcinoma, and liver transplantation states were similar to that of people with chronic liver disease.

6.7 Roche's model also included a probability of spontaneous sustained virological response in untreated children and specifically 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 non-maternally transmitted HCV. Based on the studies identified by Roche, children with maternally transmitted HCV and non-maternally transmitted HCV represented an average of 70% and 30% of the population. Roche assumed that the most common adverse effect 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 peginterferon alfa-2a related depression as

an adverse event in the economic model. Roche 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. study in adults.

6.8 Roche's base-case analysis considered treatment-naïve children and adolescents as reflected in the peginterferon alfa-2a studies. Roche presents an analysis for a subgroup of participants who do not respond and are re-treated. Roche approached the decision problem in accordance with the UK marketing authorisation for peginterferon alfa-2a. 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.

6.9 Clinical effectiveness in the base case was based on the weighted average percentages of patient who attained a sustained virological response in the Schwarz et al (PEDS-C) study and 3 uncontrolled studies: 59% for genotypes 1, 4, 5 and 6 with 48 weeks treatment and 89% for genotypes 2 and 3 with 24 weeks treatment. Roche included the cost of peginterferon alfa-2a and ribavirin as well as the cost of evaluating and monitoring patients. Roche did not include administration costs as peginterferon alfa-2a with ribavirin can be administered by the patient or a parent or carer. The drug doses depended on age, body surface area and weight, and the base-case model assumed an average dose corresponding to the dose regimen of the population in Schwarz et al. (PED-C) 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 £8,307. Roche assumed that patients did not share vials.

6.10 Roche assumed that children and adolescents who achieve a sustained virological response would not incur any costs related to

chronic HCV. A list of costs used in the model is shown in Table 14. Roche performed sensitivity analyses using assumptions from previous appraisals where sustained virological response costs were £335 and follow-up surveillance for children and adolescents whose HCV has responded in the first year were £165.

Table 13 Roche's health state costs

Health state	Mean Annual Cost
SVR	£0
Mild Chronic Hepatitis C	£178
Moderate Chronic Hepatitis C	£926
Compensated Cirrhosis	£1,470
Decompensated Cirrhosis	£11,780
Hepatocellular Carcinoma	£10,496
Liver transplantation, 1st year	£47,513
Liver transplantation, subsequent years	£1,789

6.11 For children and adolescents younger than 17 years of age, Roche applied a baseline utility of 0.95 in line with a study by Saigal et al. For the healthy population aged 17 years old and above, the model applied utility values for adults derived using an algorithm developed by Ara and Brazier In line with the EQ-5D derived utility weights used in previous health technology assessments for adults with chronic HCV. The mean utility values for sustained virological response after mild disease was 0.83, while the utility weight for having mild disease was 0.77 and 0.66 for receiving peginterferon treatment for mild disease. The mean utility values for moderate liver disease was 0.66 and 0.55 for receiving treatment for moderate disease, compared with 0.55 for compensated cirrhosis, 0.45 for both decompensated cirrhosis and hepatocellular carcinoma and 0.67 for post-liver transplantation (Table 15).

Table 14 Roche's EQ-5D derived adult utility weights from previous health technology assessments

Health state	Mean utility	Mean age	% of male
Healthy children (≤ 16 years old)	0.95	-	-
Sustained virological response after mild disease	0.83	39.8	52%
Treatment for mild disease	0.66		

Mild disease	0.77		
Treatment for moderate disease	0.55		
Moderate disease	0.66		
Cirrhosis	0.55		
Decompensated cirrhosis and HCC	0.45		
Post-liver transplantation	0.67		

Results of Roche's economic model

6.12 Table 16 presents the cost-effectiveness results for the manufacturer's base-case populations. The probability that peginterferon alfa-2a treatment was cost effective compared with best supportive care at £20,000 per QALY gained for children and adolescents with chronic HCV genotype 1, 4 or 5 treated for 48 weeks was 91.6%, and 97.2% for children and adolescents with chronic HCV genotype 2 or 3 treated for 24 weeks.

Table 15 Roche's base case results for peginterferon alfa-2a + ribavirin

Treatment	Cost (£)	Life Years	QALYs	Incremental costs, £	Incremental life years gained	Incremental QALYs	ICER (£/QALY)
Genotype 1, 4 and 5							
Best supportive care	£8199	18.47	14.20	-	-	-	-
Peginterferon alfa-2a	£12,170	18.56	15.21	£3,971	0.09	1.01	£3915
Genotype 2 and 3							
No Treatment	£8199	18.47	14.20	-	-	-	-
Peginterferon alfa-2a , 24 weeks (compared to best supportive care)	£6336	18.61	15.77	-£1864	0.14	1.57	Dominates BSC (-£1189)
Peginterferon alfa-2a, 48 weeks (compared to 24 weeks)	£11,010	18.60	15.61	£4675	-0.01	-0.16	Dominated by 24 weeks treatment (-£28878)

6.13 Roche performed one-way and 2 way deterministic analyses and found that the results were most sensitive to the time horizon, rate of disease progression, probability that a patient attained a sustained virological response with treatment, liver disease at entry, assumed health state utilities and annual cost of achieving

sustained virological response. However, the cost-effectiveness of peginterferon alfa-2a compared with best supportive care remained below £13,000 per QALY for all analyses.

MSD's economic model for peginterferon alfa-2b in combination with ribavirin

6.14 MSD submitted a de novo economic evaluation, based on previously published economic evaluations for the treatment of chronic HCV in adults. It compared the costs and health outcomes of peginterferon alfa-2a and peginterferon alfa-2b in combination with ribavirin for the treatment of children aged 3 to 17 years compared with best supportive care. The economic analysis included previously untreated children and young people aged 5 to 17 without HIV co-infection. As peginterferon alfa-2b has a licence for 3 to 4 year olds, MSD conducted an additional analysis in children aged 3 to 4 years. 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 HCV, moderate HCV or compensated cirrhosis states and receive treatment in cycle one for 12, 24 or 48 weeks depending on stopping rules (whether a patient responds during treatment) and genotype. MSD used transition probabilities from previous technology appraisals for the treatment of chronic HCV in adults; it used the same transition probabilities across all genotypes since no child-specific transition probabilities were available. The possible model states in increasing disease progression 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 assumed that the mortality risks for those in the sustained virological response, mild liver fibrosis, moderate liver fibrosis and compensated cirrhosis states were the same as for the general population. Children in the decompensated cirrhosis, hepatocellular carcinoma, and liver

transplantation state were assumed to have a higher risk of mortality than the general public.

6.15 MSD's base-case analysis considered treatment-naïve children and adolescents as reflected in peginterferon alfa-2b studies. The manufacturer approached the decision problem 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.

6.16 The evidence on the clinical effectiveness of peginterferon alfa-2a and 2b in combination with ribavirin in the base case was calculated using weighted averages of the percentage of participants responding with a sustained virological response taken from 8 trials in children and adolescents. MSD included the cost of peginterferon alfa-2a and 2b and ribavirin as well as the cost of initiating treatment, further investigation and on-treatment and post-treatment monitoring. MSD did not include costs associated with treating adverse events noting that this assumption was used in TA200 (HCV in adults) and validated by the Evidence Review Group in that appraisal. The peginterferon alfa-2a and 2b and ribavirin doses administered depended on age, body surface area and weight. The average ages at model entry were 7 (age 5-8 years represented 30.8%), 11 (age 9-13 years represented 38.5%) and 16 years (age 14-17 years represented 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's estimates of the cost of a course of treatment are summarised below in Table 17. No vial sharing was assumed.

Table 16 MSD's estimated drug acquisition costs for peginterferon alfa and ribavirin

HCV genotypes 2 or 3 (24 week treatment)		
Age	**Peginterferon alfa-2a + ribavirin (Copegus)**	**Peginterferon alfa-2b + ribavirin (Rebetol)**
3 - 4	N/A	£2400
5 - 8	£3326	£3180
9 - 13	£3628	£4370
14 - 17	£4558	£4555
HCV genotypes 1 or 4 (48 week treatment)		
3 - 4		£4800
5 - 8	£6652	£6361
9 - 13	£7256	£8740
14 - 17	£9116	£9110

6.17 MSD used health state costs presented in previous appraisals of adults as they did not identify any published evidence on costs associated with HCV in children and adolescents. MSD chose to apply the costs of sustained virological response from mild to moderate HCV for 5 years. The costs applied to sustained virological response from cirrhosis are applied over the person's lifetime. The costs associated with sustained virological response ranged from £132 to £191 per year, while the costs associated with more severe HCV were £1469 for compensated cirrhosis, £11,775 for decompensated cirrhosis, £10, 492 for hepatocellular carcinoma and £47,495 for liver transplant. The list of health states and their associated costs which MSD inflated to 2010-11 values using the Hospital and Community Health Services Pay and Price Index used in the economic model are listed in Table 18.

Table 17 MSD's list of health states and associated costs

Health state	Annual costs (in 2010-11 £)	95% Confidence intervals	Distribution and parameters
Sustained virological response from mild or moderate HCV	£132.18	£99 - £165	NA
Sustained virological response from compensated cirrhosis	£191.11	£143 - £239	NA

Mild HCV	£178	£109 - £247	Gamma k=25.70; θ=5.37
Moderate HCV	£926	£733 - £1,119	Gamma k=88.85; θ=8.07
Compensated cirrhosis	£1,469	£884 - £2,054	Gamma k=24.23; θ=46.96
Decompensated cirrhosis	£11,775	£7,930 - £15,620	Gamma k=36.03; θ=253.13
Hepatocellular carcinoma	£10,492	£5,659 - £15,325	Gamma k=18.11; θ=448.80
Liver transplant	£47,495	£33,748 - £61,242	Gamma k=89.75/13.78; θ=304.50/686.42
Post-liver transplant	£1,788	£890 - £2,686	Gamma k=15.22; θ=91.01

6.18 Because of a lack of health-related quality of life evidence for children and adolescents with chronic HCV, MSD used values for their economic analysis from published NICE technology appraisals of adults with chronic hepatitis C. The utility weights for patients with mild HCV were elicited from people with HCV participating in a study by Wright et al. using the standard EQ-5D time trade-off tariff. People receiving peginterferon alfa-2b in combination with ribavirin had a utility value of 0.77 at baseline and 0.66 when assessed at 12 and 24 weeks after starting treatment, resulting in a difference of 0.11 which was applied to all patients 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. For the remaining health states, MSD used utility values from a prospective multicentre study by Longworth et al. assessing health-related quality of life before and after liver transplant in the UK. A summary of the health state utilities used in MSD's economic analysis can be found in Table 19.

Table 18 Summary of health state utilities for MSD's cost-effectiveness analysis

Health State	Utility weight	95% CI *	Distribution and parameters
Mild HCV	0.77	0.74-0.80	Beta α=521.24; β=155.69
Moderate HCV	0.66	0.60-0.72	Beta α=168.25; β=86.67

Health State	Utility weight	95% CI *	Distribution and parameters
Compensated cirrhosis	0.55	0.45-0.65	Beta α=47.10; β=38.54
SVR from mild HCV	0.82	0.74-0.90	Beta α=65.87; β=14.46
SVR from moderate HCV	0.72	0.62-0.82	Beta α=58.06; β=22.58
SVR from compensated cirrhosis	0.61	0.51-0.71	Beta α=58.05; β=37.11
DC	0.45	0.39-0.51	Beta α=123.75; β=151.25
HCC	0.45	0.39-0.51	Beta α=123.75; β=151.25
Liver transplant	0.45	0.39-0.51	Beta α=123.75; β=151.25
Post-liver transplant	0.67	0.57-0.77	Beta α=59.25; β=29.19
Disutility because of adverse events**	0.11	NA	NA
* Ranges tested in deterministic sensitivity analyses ** Applied for treatment duration			

Results of MSD's economic model

6.19 Table 20 presents the cost-effectiveness results for MSD's base-case population (age 5-17 years). Both combinations of peginterferon alfa and ribavirin dominated best supportive care. A similar result was achieved for the 3-4 years age group. Both combinations of peginterferon alfa and ribavirin dominated best supportive care in all genotype subgroup analyses. Peginterferon alfa-2b dominated peginterferon alfa-2a in the base case analysis (all ages; -£3397/QALY) and in all subgroup analyses except in those aged between 9 and 13 years, and in children and adolescents with HCV of genotypes 1 and 4. MSD conducted deterministic sensitivity analyses around structural assumptions (time horizon, discount rates) and the model parameter values. The deterministic sensitivity analyses showed that peginterferon alfa-2b dominated best supportive care in most scenarios, except in those where the time horizon, assumed efficacy and discount rates were varied.

Table 19 MSD base case results (age 5-17 years)

	Peginterferon alfa compared to supportive care						
	Cost (£)	Life Years	QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Supportive care	£22,750	56.15	16.77	NA	NA	NA	NA
PEG alfa-2a	£17,798	63.84	19.16	-£4,952	7.69	2.39	Dominates (-£2073)
PEG alfa-2b	£17,526	64.09	19.24	-£5,224	7.94	2.47	Dominates (-£2116)

Assessment Group's critique of Roche and MSD's cost-effectiveness analyses

6.20 The Assessment Group appraised the Roche and MSD submissions for methodological quality and generalisability to the UK NHS using a checklist adapted from the NICE reference case requirements. The Assessment Group commented that the models met all of the requirements for methodological quality and generalisability, except that neither manufacturer provided evidence that their models had been validated.

6.21 The Assessment Group noted that MSD and Roche both used the state transition model applied in previous health technology assessments of peginterferon alfa treatments in adult populations. The Assessment Group considered that the model structure previously used was appropriate and it had also used the model with minor changes. The Assessment Group commented that most of the time spent in the model would be as an adult, rather than a child. Because the majority of children and adolescents start treatment (and the model) with mild chronic HCV, 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.

6.22 Both Roche and MSD conducted reviews to estimate the transition probabilities from mild-to-moderate and moderate-to-compensated cirrhosis health states. The transition probability for mild-to-moderate HCV was 0.014 per cycle in both manufacturers' submissions, while the moderate HCV to compensated cirrhosis transition probabilities differed (0.0038 from MSD and 0.021 from Roche). The Assessment Group used different transition probabilities to those from either manufacturer (see section 6.33).

6.23 The manufacturers' models used different time horizons: Roche used a time horizon of 30 years, MSD used a lifetime horizon, which was preferred by the Assessment Group. Other differences between the manufacturers' models included Roche assuming that some patients spontaneously achieve a sustained virological response, whereas MSD did not. The Assessment Group commented that the probability of spontaneous sustained virological response used by Roche was small (<2%) and unlikely to have a large impact on cost-effectiveness results. The health state utility values applied in both manufacturers' models were the same and were the same utility values applied in the previous adult chronic HCV models. Utility values for sustained virological response in the mild disease state differed slightly between the 2 submissions (0.82 and 0.83 MSD and Roche respectively) and Roche did not provide utilities for achieving a sustained virological response in the moderate disease or compensated cirrhosis health states and it is unclear from the submission whether the utility weight used for the state where sustained virological response was achieved during mild HCV was used for these 2 health states. Most health state costs used in the manufacturers' submissions were similar or the same.

Assessment Group's economic model

6.24 The Assessment Group developed an economic model estimating the cost-effectiveness of peginterferon alfa-2a and peginterferon

alfa-2b (both in combination with ribavirin) for treating chronic HCV in children and young people compared with each other and best supportive care. The perspective of the analysis was that of the NHS and PSS. 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 aim of the Assessment Group's model was to convert the probability of sustained virological response to long term survival outcomes. The Assessment Group defined treatment effectiveness in terms of probability of sustained virological response from its systematic review.

6.25 The Assessment Group adapted models used in NICE guidance TA106 and TA200 developed for the assessment of chronic HCV 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 HCV, moderate HCV and compensated cirrhosis. It did this based on evidence from Thein et al. who reviewed published rates of progression specific to stages of fibrosis progression rates based on 111 studies of individuals with chronic HCV infection (N = 33,121). The Assessment Group considered that these estimates provided the most reliable data available. In the model, people with chronic HCV 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. Sustained virological response is assumed to be permanent and nobody's HCV infection reactivates. Children and adolescents who have a sustained virological response or chronic HCV with a METAVIR score between F0 and F4 have the same mortality risks as the general population, while people with decompensated liver disease,

hepatocellular carcinoma and those who undergo liver transplantation have higher mortality rates.

6.26 The Assessment Group incorporated most of the assumptions made in the models used in previous technology appraisals including:. a person's disease stage prior to treatment influences their subsequent risk of progressive liver disease, and health-related quality of life; that people who do not achieve a sustained virological response have the same risk of disease progression as people who do not receive treatment; that the same probability of achieving a sustained virological response applies to people with mild or moderate HCV and compensated cirrhosis; that discontinuing treatment because of adverse events is not included because it is rare; and that costs associated with managing adverse events are not included as they are unlikely to be substantial. The Assessment Group included additional assumptions following discussion with experts including: that no patients would have a spontaneous sustained virological response; that a patient stops treatment at 24 weeks if they have genotype 1 or 4 and do not achieve an early virological response at week 12; and that the model includes transition probabilities, utility weights and health state costs from adults. Although the Assessment Group noted that parents' or carers' quality of life may be influenced by their child's hepatitis C, it did not find sufficient evidence to include it in the model. The Assessment Group commented that stigma associated with HCV may lower the quality of life of children and adolescents. However, the data were sparse.

6.27 The Assessment Group modelled the baseline characteristics of the populations from the clinical trials. The distribution of people across METAVIR stages of chronic HCV disease used in the model was 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).

6.28 For utility values and health state costs, the Assessment Group related health states used in previous appraisals to the METAVIR system, where mild HCV corresponds to F0 and F1 and moderate HCV corresponds to F2 and F3. The Assessment Group conducted searches to identify new evidence related to the natural history of hepatitis C in children or young people, but it found no new data.

Results of Assessment Group's economic model

6.29 Table 21 summarises the Assessment Group's probabilistic cost-effectiveness results for the base-case population for peginterferon alfa-2a and peginterferon alfa-2b in combination with ribavirin compared with best supportive care. Both peginterferon alfa-2a and peginterferon alfa-2b dominated best supportive care as they were less expensive and more effective. Treatment was more effective for genotype 2 or 3 than for genotype 1 or 4.

Table 21 Summary of Assessment Group's base case economic evaluation: peginterferon alfa-2a and peginterferon alfa-2b compared with best supportive care; and peginterferon alfa-2a compared with peginterferon alfa-2b

				Compared with BSC				PEG 2b vs. PEG 2a			
Treatment	**Costs (£)**	**LYs**	**QALYs**	**Incr. costs, £**	**Incr. LYG**	**Incr. QALY**	**ICER (£/QALY)**	**Incr. costs, £**	**Incr. LYG**	**Incr. QALY**	**ICER (£/QALY)**
All genotypes											
BSC	£29,245	22.75	20.53								
Peginterferon alfa-2a	£19,055	24.64	22.25	-£10,190	1.88	1.72	Dominates (-£5920)				
Peginterferon alfa-2b	£20,371	24.57	22.19	-£8,874	1.82	1.66	Dominates (-£5347)	£1316	-0.06	-0.06	Dominated (-£21,345)
Genotypes 1 or 4											
Best supportive care	£29,245	22.75	20.53								
Peginterferon alfa-2a	£21,278	24.39	22.00	-£7,967	1.63	1.47	Dominates (-£5402)				
Peginterferon alfa-2b	£22,316	24.35	21.97	-£6,929	1.60	1.44	Dominates (-£4799)	£1038	-0.03	-0.03	Dominated (£-33,675)
Genotypes 2 or 3											
Peginterferon alfa-2a	£11,831	25.45	23.05	-£17,414	2.70	2.52	Dominates (-£6903)				
Peginterferon alfa-2b	£11,202	25.61	23.21	-£18,043	2.85	2.68	Dominates (-£6740)	-£629	0.16	0.15	Dominates (-£4082)

6.30 The Assessment Group's base case results for peginterferon alfa-2a compared with peginterferon alfa-2b are presented in Table 21. In the base case (including all genotypes) 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). In the genotype 1 or 4 subgroup, peginterferon alfa-2a was also less costly and more effective than peginterferon alfa-2b (£21,278 compared with £22,316 and 24.39 QALYs compared with 24.35 QALYs). However, peginterferon alfa-2a cost more and was less effective than peginterferon alfa-2b (£11,831 compared with £11,202 and 23.05 QALYs compared with 23.21 QALYs) for those with genotype 2 or 3. The Assessment Group commented that the differences between treatments were marginal. 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.

6.31 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), sustained virological responses for peginterferon alfa-2a (69% and 51%) and peginterferon alfa-2b (65% and 52%), degree of liver pathology (100% F0, 100% F2, 100% F3 and 20% F4), starting age (5 years and 16 years), transition probabilities (lower CI and upper CI), utility values (lower CI, upper CI and previous appraisal), and health state costs (lower CI and upper CI). In all analyses, best supportive care was dominated by both peginterferon alfa-2a and peginterferon alfa-2b. The Assessment Group commented that one should treat the deterministic

sensitivity analysis for peginterferon alfa-2b compared with peginterferon alfa-2a with caution because of uncertainty around the relative treatment effect. The analyses showed that the model was most sensitive to changes in treatment effectiveness. 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 for sustained virological response (peginterferon alfa-2a 51% or peginterferon alfa-2b 65%) and the starting age of the cohort (age 5 years).

6.32 The Assessment Group conducted 3 scenario analyses around structural assumptions. The first investigated the rates for sustained virological response for peginterferon alfa-2b compared with peginterferon alfa-2a. For the base case, the sustained virological response rate for peginterferon alfa-2b was 58% and for peginterferon alfa-2a it was 60%. The Assessment Group varied the sustained virological response rate for peginterferon alfa-2b to between 50% and 70%, keeping the sustained virological rate for peginterferon alfa-2a at 60%. The results showed that the cost effectiveness of peginterferon alfa-2a compared with peginterferon alfa-2b is proportionate to the relative sustained virological response rate of the treatments. In the scenarios where the sustained virological response rate for peginterferon alfa-2a was greater than or equal to peginterferon alfa-2b, peginterferon alfa-2a was the most cost-effective treatment. In scenarios where the sustained virological response rate for peginterferon alfa-2b was greater than for peginterferon alfa-2a, peginterferon alfa-2b was the most cost-effective treatment.

6.33 The second scenario analysis varied the transition probabilities between the chronic HCV health states (F0- F3) to the decompensated cirrhosis health state F4. The Assessment Group varied 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. In the base case, people spent a mean duration of 28.7 years in the F0 to F3 states. In the scenario analysis, the time spent in the chronic HCV health states varied between 10 and 48 years resulting in best supportive care costs ranging between £19,797 (48 years) and £41,859 (10 years). Peginterferon alfa-2a treatment costs ranged between £15,091 and £24,321 dominating 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 HCV state.

6.34 The third scenario analysis assessed the impact of delaying peginterferon alfa-2a treatment until adulthood (aged 18 to 30 years) instead of initiating it during childhood. The Assessment Group commented that this 'watchful waiting' strategy was associated with higher costs (between £21,959 and £26,668) and 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.

6.35 The Assessment Group also conducted probabilistic sensitivity analysis for the following parameters: the proportion of children with a given genotype, transition probabilities, health state utilities and monitoring, health state and treatment costs. The probabilistic sensitivity analysis results closely reflect those from the deterministic base case results (Table 22). The probability that peginterferon alfa-2a and 2b are cost effective at £20,000 and £30,000 per QALY gained is 68% and 66% for peginterferon alfa-2a and 32% and 34% for peginterferon alfa-2b, respectively.

Table 22 Assessment Group's base case probabilistic sensitivity analysis results

Treatment	Costs (£) interquartile range (25% and 75%)	QALYs interquartile range (25% and 75%)	Compared to	
			best supportive care	peginterferon alfa-2a
Best supportive care	£29,689 (£26,958 -£31,979)	20.50 (20.1 – 21.0)	-	-
Peginterferon alfa-2a	£19,226 (£17,679 - £20,593)	22.22 (22.0 – 22.5)	dominates	-
Peginterferon alfa-2b	£20,558 (£19,202 - £21,777)	22.16 (21.9 – 22.4)	dominates	dominated

Comparison of the Assessment Group and manufacturer's models

6.36 The Assessment Group compared its results with those of the manufacturers (summarised in Table 23). The Assessment Group commented that the 3 models all found that peginterferon alfa-2a and peginterferon alfa-2b (each in combination with 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 with the interpretation of results as the differences were marginal. The costs and QALY estimates used in each evaluation varied between analyses. The differences in costs were based on the use of a shorter time horizon (in the case of Roche's submission) or the length of time spent in HCV health states (shorter in the Assessment Group's analysis compared with MSD's submission). The differences in QALY estimates were also based on the use of a shorter time horizon (in the case of Roche's submission) and the lower utility values used in the MSD submission compared with the Assessment Group's model.

Table 20 Comparison of manufacturers' and Assessment Group's cost effectiveness results

	Analysis	Best supportive care	Peginterferon alfa-2a	Peginterferon alfa-2b
Total cost, £	Assessment Group, all genotypes	£29,245	£19,055	£20,371
	MSD, all genotypes	£22,750	£17,798	£17,526
	Roche, genotype 1 and 4	£8,199	£12,170	-
	Roche, genotype 2 and 3	£8,199	£6,336	-
Total QALY	Assessment Group	20.53	22.25	22.19
	MSD, all genotypes	16.77	19.16	19.24
	Roche, genotype 1 and 4	14.20	15.21	-
	Roche, genotype 2 and 3	14.20	15.77	-
Incremental cost vs best supportive care, £	Assessment Group, all genotypes	-	-£10,190	-£8,874
	MSD, all genotypes	-	-£4,952	-£5,224
	Roche, genotype 1 and 4	-	£3,971	-
	Roche, genotype 2 and 3	-	-£1,864	-
Incremental QALY vs best supportive care	Assessment Group, all genotypes	-	1.72	1.66
	MSD, all patients	-	2.39	2.47
	Roche, genotype 1 and 4	-	1.01	-
	Roche, genotype 2 and 3	-	1.57	-
ICER vs best supportive care £ per QALY	Assessment Group, all genotypes	-	Dominates (-£5920)	Dominates (-£5347)
	MSD, all patients	-	Dominates (-£2073)	Dominates (-£2116)
	Roche, genotype 1 and 4	-	£3,915	-
	Roche, genotype 2 and 3	-	Dominates (-£1189)	-
ICER peginterferon alfa-2b vs peginterferon alfa-2a, £ per QALY	Assessment Group, all genotypes	-	-	Dominated (-£21,345)
	Assessment Group, genotype 1 and 4			Dominated (-£33,675)
	Assessment Group, genotype 2 and 3			Dominates (-£4082)
	MSD, all genotypes	-	-	Dominates (-£3397)
	Roche, genotype 1 and 4	-	-	-
	Roche, genotype 2 and 3	-	-	-

7 Equalities issues

7.1 During the scoping consultation, it was suggested that young people who misuse drugs recent immigrants and asylum seeker who are children 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.

8 Innovation

Roche

8.1 Roche commented that pegylated interferons have existed for over 15 years, so peginterferon alfa-2a would not be considered an innovative medicine but instead is an additional option available to physicians, patients, and caregivers when considering treatments for HCV.

Merck Sharp and Dohme

8.2 MSD commented that peginterferon alfa-2a and alfa-2b and ribavirin were innovative therapies for the treatment of chronic HCV in adults when first launched and that the extension of the marketing authorisation to children and adolescents means that this innovation now applies to younger patients. Peginterferon alfa-2a and alfa-2b are dosed once weekly, compared to the thrice weekly dosing of interferon alfa, thus reducing the burden of the treatment for patients.

8.3 MSD believe that successful treatment of chronic HCV in children will have an impact on the childrens' carers, and this would not be captured by the QALY calculation. MSD cited a study reporting that hepatitis C among children is associated with increased caregiver stress, and a study conducted in Australia indicating substantial quality of life benefits for parents and caregivers as a result of the child achieving sustained virological response.

8.4 MSD also commented that sustained virological response in children and adolescents with chronic HCV also prevents onwards transmission of the virus, therefore reducing the pool of infected individuals with HCV in the UK.

9 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Telaprevir for the treatment of genotype 1 chronic hepatitis C. NICE technology appraisal guidance 252 (2012). Available from www.nice.org.uk/guidance/TA252
- Boceprevir for the treatment of genotype 1 chronic hepatitis C. NICE technology appraisal guidance 253 (2012). Available from www.nice.org.uk/guidance/TA253
- 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). Available from www.nice.org.uk/guidance/TA200
- Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C (extension of technology appraisal guidance 75). NICE technology appraisal guidance 106 (2006). Available from www.nice.org.uk/guidance/TA106
- 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). Available from www.nice.org.uk/guidance/TA75
- Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection. NICE public health guidance 43 (2012). Available at www.nice.org.uk/guidance/PH43

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

- There is a NICE pathway on Hepatitis B and C testing overview, which is available from http://pathways.nice.org.uk/pathways/hepatitis-b-and-c-testing

Appendix B: Clinical efficacy section of the draft European public assessment report

EPAR for Peginterferon alfa-2a (Pegasys, Roche),
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000395/WC500140705.pdf

SPC for Peginterferon alfa-2a (Pegasys, Roche),
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000395/WC500039195.pdf

EPAR for Ribavirin (Copegus, Roche),
http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&ssDocName=CON137709

SPC for Ribavirin (Copegus, Roche),
http://www.medicines.org.uk/emc/medicine/11755/SPC/Copegus+200mg+and+400mg+Film-coated+Tablets/

EPAR for Peginterferon alfa-2b (ViraferonPeg, Merck Sharp and Dohme),
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000329/WC500064054.pdf

SPC for Peginterferon alfa-2b (ViraferonPeg, Merck Sharp and Dohme),
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000329/WC500051384.pdf

EPAR for Ribavirin (Rebetol, Merck Sharp and Dohme),
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion_-_Variation/human/000246/WC500048392.pdf

SPC for Ribavirin (Rebetol, Merck Sharp and Dohme),
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000246/WC500048210.pdf