

# Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C

Technology appraisal guidance

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## Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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This guidance partially replaces TA75 and TA106.

## 1 Guidance

This guidance should be read in conjunction with the following NICE guidance:

- NICE technology appraisal guidance 75 (TA75) '[Interferon alfa \(pegylated and non-pegylated\) and ribavirin for the treatment of chronic hepatitis C](#)' (which covers moderate to severe hepatitis C)
- NICE technology appraisal guidance 106 (TA106) '[Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C](#)'.

This appraisal addresses extensions to the marketing authorisations for peginterferon alfa-2a and peginterferon alfa-2b. This guidance updates and replaces:

- section 1.2, bullet 3 only, of TA75
- section 1.4 of TA75 for adults who are eligible for shortened courses of combination therapy (as described in section 1.2 of the current guidance)
- section 1.7, bullet 1 only, of TA75
- sections 1.4 and 1.5 of TA106.

All other recommendations in TA75 and TA106 still stand.

- 1.1 Combination therapy with peginterferon alfa (2a or 2b) and ribavirin is recommended as a treatment option for adults with chronic hepatitis C:
- who have been treated previously with peginterferon alfa (2a or 2b) and ribavirin in combination, or with peginterferon alfa monotherapy, and whose condition either did not respond to treatment or responded initially to treatment but subsequently relapsed or
  - who are co-infected with HIV.
- 1.2 Shortened courses of combination therapy with peginterferon alfa (2a or 2b) and ribavirin are recommended for the treatment of adults with chronic

hepatitis C who:

- have a rapid virological response to treatment at week 4 that is identified by a highly sensitive test **and**
- are considered suitable for a shortened course of treatment.

1.3 When deciding on the duration of combination therapy, clinicians should take into account the licensed indication of the chosen drug (peginterferon alfa-2a or peginterferon alfa-2b), the genotype of the hepatitis C virus, the viral load at the start of treatment and the response to treatment (as indicated by the viral load).

## 2 Clinical need and practice

- 2.1 Hepatitis C is an infectious disease of the liver caused by the hepatitis C virus (HCV). The virus is acquired primarily through percutaneous exposure to contaminated blood. People infected with HCV are often asymptomatic, but about 20% develop acute hepatitis. In approximately 80% of people who are infected, the virus is not cleared and they go on to develop chronic hepatitis C. Chronic hepatitis C is categorised as mild, moderate or severe depending on the extent of liver damage. The rate of progression from mild to severe disease is slow but variable, taking about 20 to 50 years from the time of infection. About 30% of infected people develop cirrhosis within 20 to 30 years, and some of these develop hepatocellular carcinoma. Some people with end-stage liver disease or hepatocellular carcinoma may require liver transplantation.
- 2.2 Estimates from the Health Protection Agency suggest that approximately 142,000 people between the ages of 15 and 59 years had chronic HCV infection in England and Wales in 2003, a prevalence of 0.44% in this age group. The prevalence of chronic HCV infection varies by sex and age, and it is most common in men and in people aged 25 to 44 years. In 2007, the number of confirmed new HCV infections in England and Wales was 7540.
- 2.3 Six genetic types of HCV, known as genotypes, have been found. Genotype 1 is the most common in the UK, accounting for about 40% to 50% of those infected with HCV. Genotypes 2 and 3 together contribute another 40% to 50%, while genotypes 4, 5 and 6 account for the remaining infections. In England and Wales, genotypes 1 and 3 represent more than 90% of all diagnosed HCV infections.
- 2.4 The primary aim of treatment is to clear the virus from the blood. Successful treatment is usually indicated by a sustained virological response, which is defined as undetectable serum HCV RNA 6 months after the end of treatment. A sustained virological response is considered to indicate permanent resolution of infection, although relapse may occur in approximately 5% of people after 5 years.
- 2.5 Previous NICE guidance (TA106 and TA75) recommends combination therapy with ribavirin and either peginterferon alfa-2a or peginterferon alfa-2b for adults with chronic hepatitis C. The previous guidance also recommends that

monotherapy with peginterferon alfa-2a or peginterferon alfa-2b should be used only by people who are unable to tolerate ribavirin or for whom ribavirin is contraindicated. The recommended duration of treatment is 24 or 48 weeks depending on a combination of factors, including the HCV genotype, the viral load at the start of treatment and whether a person has a rapid virological response to treatment. For people with mild HCV infection, the person and their clinician should decide whether to treat immediately or adopt an approach of 'watchful waiting' (see TA106). The use of peginterferon alfa and ribavirin combination therapy is also considered suitable for people who are co-infected with HCV and HIV, unless it is contraindicated.

- 2.6 Approximately 75% to 85% of people with moderate or severe infection with HCV genotype 2 or 3 have a sustained virological response 6 months after finishing a course of treatment with peginterferon alfa plus ribavirin. The proportion of people with HCV genotype 1 who show a sustained virological response after the end of treatment is about 40% to 50%, while for the other genotypes (4, 5 and 6) the proportion is generally reported to be between 50% and 75%. Clinical advice indicates that a substantial proportion of people treated in specialist clinics in England and Wales have had previous treatment, but their condition has not responded or has relapsed.

### 3 The technologies

#### *Peginterferon alfa-2a*

- 3.1 Peginterferon alfa-2a (Pegasys, Roche Products) has a UK marketing authorisation for 'the treatment of chronic hepatitis C in adult patients who are positive for serum HCV-RNA, including patients with compensated cirrhosis and/or who are co-infected with clinically stable HIV'. The preferred treatment regimen is in combination with ribavirin, but monotherapy is indicated in cases of intolerance or contraindication to ribavirin. Patients may not have been previously treated or their condition may have not responded to previous treatment with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin. The recommended dose is 180 micrograms once a week, administered subcutaneously, for 16, 24 or 48 weeks depending on HCV genotype, baseline viral load and response to treatment. The recommended duration of peginterferon alfa-2a monotherapy is 48 weeks.
- 3.2 When peginterferon alfa-2a is given in combination with ribavirin, people with HCV genotype 1 or 4 infections who have detectable HCV RNA at week 4 (that is, there is not a rapid virological response) should receive 48 weeks of treatment. People with genotype 2 or 3 infections and undetectable HCV RNA at week 4 (that is, a rapid virological response) should receive 24 weeks of treatment.
- 3.3 An extension to the licence for peginterferon alfa-2a now means that some people with hepatitis C are eligible for shortened courses of treatment. People with HCV genotype 1 and a low viral load (equal to or less than 800,000 IU/ml) at the start of treatment, a rapid virological response at week 4 and undetectable HCV RNA at week 24 may complete treatment at week 24 rather than receiving the standard 48 weeks of therapy. The licence extension also allows people with HCV genotype 2 or 3 who have a low viral load (equal to or less than 800,000 IU/ml), undetectable HCV RNA by week 4 (that is, a rapid virological response) and undetectable HCV RNA at week 16 to stop treatment at week 16 rather than receiving the standard 24 weeks of therapy. People with HCV genotype 4 may be treated in line with the regimen for people with genotype 1, but without requiring a low viral load. People with genotype 5 or 6 should be treated for 48 weeks. People co-infected with HIV should also be treated for 48 weeks, regardless of genotype.



- 3.4 Re-treatment with peginterferon alfa-2a plus ribavirin may be offered to people whose hepatitis C has not shown an adequate response to treatment (non-response) or has responded but subsequently relapsed. Re-treated people should receive 48 weeks of treatment unless HCV RNA is still detectable at week 12, in which case treatment should be stopped. People with HCV genotype 1 whose condition has not responded to prior treatment with peginterferon alfa and ribavirin combination therapy and who are considered for re-treatment should receive 72 weeks of combination therapy.
- 3.5 A weekly course of treatment with peginterferon alfa-2a (180 micrograms) costs £126.91 (excluding VAT; British national formulary [BNF] edition 59). Costs may vary in different settings because of negotiated procurement discounts.

### *Peginterferon alfa-2b*

- 3.6 Peginterferon alfa-2b (ViraferonPeg, Schering-Plough) has a UK marketing authorisation for 'the treatment of adult patients with chronic hepatitis C who are positive for HCV-RNA, including patients with compensated cirrhosis and/or co-infected with clinically stable HIV'. The preferred treatment regimen is in combination with ribavirin, but monotherapy with peginterferon alfa-2b is indicated in cases of intolerance or contraindication to ribavirin. Patients may not have been treated previously or their condition may have not responded to previous treatment with interferon alpha (pegylated or non-pegylated) in combination with ribavirin or interferon alfa monotherapy.
- 3.7 The recommended dose of peginterferon alfa-2b is 1.5 micrograms/kg body weight once a week, administered subcutaneously, for 24 or 48 weeks depending on HCV genotype, viral load at the start of treatment and response to treatment. People with HCV genotype 1 who have undetectable HCV RNA at week 12 (that is, who have an early virological response) should receive 48 weeks of treatment with peginterferon alfa-2b. People with a genotype 1 infection without an early virological response are considered unlikely to have a sustained virological response, and consideration should be given to withdrawing treatment. People with HCV genotype 4 should be treated with the same regimen as for genotype 1 infections. People with HCV genotype 2 or 3 infections should be treated for 24 weeks. People co-infected with HIV should be treated for 48 weeks regardless of HCV genotype.

- 3.8 Following a licence extension for peginterferon alfa-2b, some people with hepatitis C are eligible for shortened courses of treatment. People with HCV genotype 1 and a low viral load (below 600,000 IU/ml) at the onset of treatment and who have undetectable HCV RNA at both week 4 and week 24 of treatment can stop treatment at 24 weeks. The marketing authorisation notes that a shortened course of 24 weeks of treatment may be associated with a higher risk of relapse than if treatment is given for 48 weeks. The marketing authorisation does not permit shorter treatment durations for people with HCV genotype 2 or 3 infections.
- 3.9 Re-treatment with peginterferon alfa-2b in combination with ribavirin is recommended in the marketing authorisation for people whose hepatitis C has not shown an adequate response to treatment (non-response) or has responded but subsequently relapsed. All people re-treated with peginterferon alfa-2b, irrespective of HCV genotype, who have undetectable serum HCV RNA at week 12 should receive 48 weeks of treatment. People re-treated with peginterferon alfa-2b in whom HCV RNA is still detectable at week 12 are unlikely to have a sustained virological response after 48 weeks of therapy.
- 3.10 A weekly course of peginterferon alfa-2b (average of 120 micrograms) costs £162.60 (excluding VAT; BNF 59). Costs may vary in different settings because of negotiated procurement discounts.

## *Ribavirin*

- 3.11 Two forms of ribavirin (Copegus, Roche Products; Rebetol, Schering-Plough) are currently available. Each product is indicated for the treatment of chronic hepatitis C and must be used only as part of a combination regimen with peginterferon alfa or interferon alfa. Ribavirin monotherapy must not be used. Each product is licensed for use only in combination with the interferon products made by the same manufacturer. The recommended doses of ribavirin range from 800 to 1400 milligrams, depending on body weight. The dose of Copegus also varies according to HCV genotype: 800 milligrams per day for genotype 2 or 3 infections and 1000 or 1200 milligrams per day for genotype 1, 4, 5 or 6 infections (1000 milligrams for body weights below 75 kg and 1200 milligrams for body weights of 75 kg or more). Both forms of ribavirin are taken orally each day in two divided doses.

- 3.12 The weekly cost of Copegus is £111 for HCV genotype 1 infections (based on 1200 milligrams per day for an average body weight of 79 kg) and £74 for HCV genotype 2 or 3 infections (based on 800 milligrams per day). The weekly cost of Rebetol is £68, based on 1000 milligrams per day for an average body weight of 79 kg. Costs exclude VAT and are from BNF 59. Costs may vary in different settings because of negotiated procurement discounts.

### *Costs of combination treatment*

- 3.13 The cost of treatment with peginterferon alfa-2a plus ribavirin (Copegus) is estimated to be £3215 for 16 weeks or £4824 for 24 weeks of therapy (for people with genotypes 2 or 3), or £11,425 for 48 weeks of therapy (for people with genotypes 1 or 4). For people treated with peginterferon alfa-2b plus ribavirin (Rebetol), the cost is £5540 for 24 weeks or £11,081 for 48 weeks of therapy (for people with genotype 1). Acquisition costs are from BNF 59. Costs may vary in different settings because of negotiated procurement discounts.

### *Adverse effects of treatment*

- 3.14 The most common adverse effects associated with peginterferon-based anti-viral treatments include influenza-like symptoms such as headache, fatigue and fever, as well as insomnia, anorexia, dermatological symptoms, nausea, vomiting and depression. The adverse effects of anti-viral treatment for HCV, notably depression, may be more pronounced in people co-infected with HIV. For full details of adverse effects and contraindications, see the summaries of product characteristics.

## 4 Evidence and interpretation

The Appraisal Committee ([appendix A](#)) considered evidence from a number of sources ([appendix B](#)).

### 4.1 *Clinical effectiveness*

4.1.1 The Assessment Group performed a systematic review to identify randomised controlled trials (RCTs) evaluating the clinical effectiveness of peginterferon alfa plus ribavirin for the treatment of chronic hepatitis C in three specific groups:

- people eligible for shortened treatment courses
- people eligible for re-treatment following previous non-response or relapse of their condition
- people co-infected with HCV and HIV.

Included in the review were studies in which a standard duration of combination therapy with peginterferon alfa plus ribavirin (or peginterferon monotherapy for people with contraindications to ribavirin) was compared with courses of combination therapy of a shortened duration (24 weeks for people with HCV genotype 1 treated with either peginterferon alfa-2a or -2b; 16 weeks for people with HCV genotype 2 or 3 treated with peginterferon alfa-2a only). The review also attempted to identify studies in which treatment was compared with best supportive care for subgroups that were co-infected with HIV or were being re-treated. Clinical outcomes included measures of virological response during and after treatment, and adverse effects.

4.1.2 Six RCTs reported in eight publications were identified, all of which reported on peginterferon alfa and ribavirin combination therapy in people eligible for shortened courses of treatment. No studies were found that compared treatment with peginterferon alfa (with or without ribavirin) with best supportive care for people co-infected with HIV and HCV or for people whose hepatitis C had not responded to previous treatment or had responded but subsequently relapsed.

## Shortened treatment courses

- 4.1.3 Of the six trials, four evaluated the effect of shortened treatment courses with peginterferon alfa plus ribavirin for people with HCV genotype 1 infections, while the other two trials evaluated the effect for people with genotype 2 or 3 infections. No trials assessed the effect of shortened treatment courses for people with genotype 4 infections. Five of the trials included people with a low viral load at the start of treatment. The comparator in all included studies was the same intervention for a standard duration of treatment. The dose of peginterferon alfa-2a was 180 micrograms per week and the dose of peginterferon alfa-2b was 1.5 micrograms per kg per week in all trials. All six RCTs reported sustained virological response rates as the primary outcome measure. A sustained virological response was defined as undetectable serum HCV RNA at the end of 24 weeks' follow-up in four trials, and as undetectable serum HCV RNA at the end of treatment and at the end of follow-up in the other two trials. In many of the trials the sustained virological response rates were presented for subgroups of people who had been randomised and who achieved a rapid virological response. It was not reported whether these subgroups were powered to detect a statistically significant difference between trial arms. A rapid virological response was defined as an undetectable serum concentration of HCV RNA (25 IU/ml or less) in one trial, serum HCV RNA negative (50 IU/ml or less) in three trials, serum HCV RNA of 600 IU/ml or less in one trial, and serum HCV RNA of 650 IU/ml or less in one trial, all at week 4 of treatment.
- 4.1.4 In people with a low viral load (800,000 IU/ml or less) who attained a rapid virological response up to and including week 4 of treatment, sustained virological response rates were comparable between the group that received 48 weeks (standard duration) of treatment (range 83% to 100%) and the group that received shortened treatment courses (range 84% to 96%), with no statistically significant differences between the groups. Regardless of HCV genotype, sustained virological response rates were similar across studies, with the exception of one trial that reported lower rates.
- 4.1.5 In two of the trials of peginterferon alfa-2a plus ribavirin, the ribavirin dose was varied according to body weight, which is no longer consistent with its marketing authorisation. The marketing authorisation specifies that ribavirin should be given as a fixed dose of 800 milligrams in people with HCV genotype 2

or 3, and both trials assessed the effectiveness of treatment only in people with HCV genotype 2 or 3 infections. The Assessment Group noted that if these two trials had been excluded on the basis of the variable ribavirin dosages, there would have been no evidence on the impact of shortened treatment durations in people with HCV genotype 2 or 3 infections.

- 4.1.6 Rapid virological response rates were comparable between the groups that received the standard duration of treatment and those that received shortened courses. However, there was a large range in reported rapid virological response rates between the studies, with rates in people with HCV genotype 2 or 3 infections generally being higher than those in people with genotype 1 infections.
- 4.1.7 The relapse rate in a subgroup of people with a low viral load and a rapid virological response was reported in one trial. Relapse was defined as the re-appearance of serum HCV RNA during the 24-week follow-up period in people whose condition initially responded to treatment. The rates of relapse were low and were not statistically significantly different between the treatment arms (3.6% for 24 weeks of treatment versus 0% for 48 weeks of treatment;  $p = 1.00$ ). In contrast, in people with a high viral load at start of treatment and a rapid virological response later, shortening the duration of treatment was associated with a statistically significant higher rate of relapse (23.5% for 24 weeks versus 0% for 48 weeks;  $p = 0.045$ ).
- 4.1.8 Adverse events were presented for treatment groups as a whole, and not for the subgroup of people with a low viral load who had a rapid virological response. Overall, the frequency of adverse events did not differ statistically between treatment arms, although a lower incidence of adverse events was reported in three trials in people treated for a shorter duration with combination therapy. The most frequently occurring adverse events included influenza-like symptoms, insomnia, anorexia, dermatological symptoms and alopecia.
- 4.1.9 The cumulative incidence of serious adverse events ranged from 0% to 7% over the duration of the trials, and was not considered to be substantially different between treatment arms, although levels of statistical significance were lacking in most studies. One death was reported, which was a result of re-activation of pulmonary tuberculosis at week 36 of treatment in a person who was treated with peginterferon alfa-2a plus ribavirin. One trial reported that people

receiving a shortened treatment regimen were less likely to discontinue their treatment than people receiving longer courses (3% versus 10%;  $p = 0.045$ ).

## Re-treatment after non-response or relapse

4.1.10 The Assessment Group did not identify any RCTs that compared treatment with peginterferon alfa (with or without ribavirin) with best supportive care for people whose hepatitis C had not responded to previous treatment or had responded but subsequently relapsed. The Assessment Group did identify a number of RCTs comparing treatment with peginterferon alfa (with or without ribavirin) with active treatment comparators (such as non-peginterferon alfa plus ribavirin), but these did not meet the inclusion criteria for the review (based on the decision problem) because they featured an active treatment comparator. However, the Assessment Group assumed in its economic model (see section 4.2) that the sustained virological response rates for people whose condition did not respond or responded but subsequently relapsed on peginterferon alfa therapy were those reported in the clinical trials that used an active comparator. The Assessment Group noted that these reported sustained virological response rates may not be representative of people with relapsed disease because the trial participants with HCV genotype 1 infections had less intensive initial treatment than what would be regarded as standard treatment.

## HCV and HIV co-infection

4.1.11 The Assessment Group did not identify any RCTs that compared treatment with peginterferon alfa (with or without ribavirin) with best supportive care for people with HCV and HIV co-infection. A number of RCTs were identified that compared peginterferon alfa (with or without ribavirin) with active treatment comparators (such as non-peginterferon alfa plus ribavirin) for this subgroup, but these did not meet the inclusion criteria for the review because they featured an active treatment comparator. The Assessment Group noted that it is unlikely that any studies, whether randomised or not, would be available that include a non-active treatment arm, because withholding treatment would be unlikely to be considered ethical.

## Summary of clinical-effectiveness evidence

4.1.12 The collective evidence for combination therapy for both peginterferon alfa-2a and peginterferon alfa-2b suggests that there are no statistically significant

differences in sustained virological response rates between people receiving shortened durations of treatment with peginterferon alfa plus ribavirin of 16 weeks (HCV genotype 2 or 3; peginterferon alfa-2a) or 24 weeks (HCV genotype 1; both peginterferon alfa-2a and alfa-2b) and people receiving the standard duration of treatment. Rates of relapse following a shortened course of treatment were reported to be low and not statistically significantly different from relapse rates after a standard course of treatment in people with a rapid virological response and low viral load. For people with a rapid virological response and a high viral load, shortening the duration of treatment may be associated with a higher rate of relapse. However, the Assessment Group noted that analyses of sustained virological responses in people with a low viral load at the start of treatment and a rapid virological response are likely to be underpowered because they were based on subgroups of the randomised participants, and therefore the results should be interpreted with caution. No RCTs were identified that compared peginterferon alfa (with or without ribavirin) with best supportive care for people who were re-treated after non-response or relapse of their condition, or for people with HCV and HIV co-infection.

## 4.2 *Cost effectiveness*

- 4.2.1 The Assessment Group identified two studies examining the cost effectiveness of the treatment of people co-infected with HCV and HIV. The studies compared peginterferon alfa plus ribavirin with non-peginterferon plus ribavirin, peginterferon alfa monotherapy and no treatment (supportive care). One study also had an additional non-peginterferon alfa monotherapy arm. No economic evaluations were identified for people requiring re-treatment following previous non-response or relapse, or for people eligible for shortened courses of treatment.
- 4.2.2 In both studies of people co-infected with HCV and HIV, peginterferon alfa monotherapy or peginterferon alfa plus ribavirin dominated (that is, treatment was more effective and less costly) the other strategies in people with HCV genotype 1. In one study, peginterferon alfa monotherapy was the most favourable option in each scenario. For people with other HCV genotypes (that is, not genotype 1), peginterferon alfa plus ribavirin was the least favourable option in one study (incremental cost-effectiveness ratios [ICERs] of \$300,800 to \$4,000,000 per quality-adjusted life year [QALY] gained). In the second study



peginterferon alfa plus ribavirin dominated the other strategies for all genotypes reported. The incremental costs per life year saved (LYS) for peginterferon alfa plus ribavirin in people with HCV genotypes other than genotype 1 were \$39,300/LYS in women and \$39,700/LYS in men and \$70,000/LYS in women and \$73,000/LYS in men in people with genotype 1).

## Manufacturers' models

### *Roche Products*

- 4.2.3 A health state transition model submitted by Roche Products was used to assess the cost effectiveness of treatment with peginterferon alfa-2a plus ribavirin in three groups: people who had been treated previously with peginterferon alfa plus ribavirin, including those whose hepatitis C did not respond to this previous treatment (by HCV genotype) and those whose condition responded but then relapsed; people with a low viral load and a rapid virological response who received shortened courses of peginterferon alfa plus ribavirin (by genotype); and people co-infected with HCV and HIV.
- 4.2.4 The model used clinical-effectiveness data from published RCTs, although evidence of effectiveness for shortened treatment courses was derived from subgroup analyses. For people receiving shortened treatment courses, the sustained virological response rates for both groups in the model were taken from unpublished analyses of subgroups of clinical trial participants. For the subgroups with HCV genotypes 2 and 3 the data were taken from the ACCELERATE study reported by Shiffman and colleagues, and for the genotype 1 and 4 subgroups the data were taken from a trial reported by Hadziyannis and colleagues (study NV15942).
- 4.2.5 A number of the clinical-effectiveness studies used by the manufacturer to obtain data for the economic model (namely for people who had been re-treated or had HIV co-infection) had active comparators, rather than comparing treatment with best supportive care (as outlined in the decision problem). For people with HCV and HIV co-infection, data on sustained virological response rates were taken from a clinical trial comparing non-peginterferon alfa-2a with peginterferon alfa-2a, which is not consistent with the scope for this appraisal. For people whose hepatitis C did not respond or relapsed on previous peginterferon therapy, data on sustained virological response rates were taken from two clinical trials. In the majority of situations it was assumed that people

receiving best supportive care would not achieve a spontaneous sustained virological response. No discussion or critical analysis of the reliability or generalisability of the clinical-effectiveness evidence used to populate the model was provided by the manufacturer.

- 4.2.6 Shortening the duration of treatment was associated with a QALY loss compared with the standard treatment duration (because of a slight reduction in the sustained virological response rate), as well as with a reduction in costs. Since both costs and outcomes were lower with shortened treatment duration, the ICERs represent savings per QALY lost. For people with HCV genotype 1 or 4 the ICER was £15,472 per QALY, and for people with genotype 2 or 3 the ICER was £2719 per QALY. The Assessment Group noted that when there are both lower costs and lower effectiveness, the analysis can be better understood by applying the net benefits framework. Using the net benefits framework, a treatment would be accepted when the value of the incremental benefits exceeds the incremental costs, resulting in a positive incremental net benefit. Using this framework, the incremental net monetary benefit for a shortened duration of treatment is positive for people with HCV genotype 1 or 4 over a wide range of willingness-to-pay values (below the ICER value of £15,472 per QALY). For people with HCV genotype 2 or 3 the incremental net monetary benefit is positive only at comparatively low threshold values (below the ICER value of £2719 per QALY).
- 4.2.7 Re-treating people whose hepatitis C relapsed following previous peginterferon treatment was reported by the manufacturer as dominating best supportive care. This is the result of including a high sustained virological response rate observed in one trial that may not be generalisable to other populations of people whose condition relapses. The majority of people had HCV genotype 1 infections and their previous treatment was of shorter duration than the current standard of care (that is, 24 weeks rather than 48 weeks). The sustained virological response rates applied in the model for the re-treatment of people whose hepatitis C had not responded to previous peginterferon treatment were lower than those for people whose condition had relapsed following treatment. Treatment was associated with QALY gains and increased costs compared with best supportive care, resulting in ICERs of £3334 per QALY gained for people with HCV genotype 1 and £809 per QALY gained for people with other genotypes. The majority of people recruited to the trial whose condition did not respond to previous peginterferon treatment had HCV genotype 1; only 29

were infected with other HCV genotypes (9% of the arm used to estimate the effectiveness of treatment in the model), and the majority (66%) of these had genotype 4 infections.

4.2.8 For people with HCV and HIV co-infection, treatment with peginterferon plus ribavirin was estimated to dominate treatment with non-peginterferon. However, this is not the comparison specified in the decision problem issued by NICE (where best supportive care was stated as the comparator). The Assessment Group extended the analysis by assuming that the sustained virological response rate for untreated people would be zero, and estimated a QALY gain (using the manufacturer's model) of 1.95 and an incremental cost of £1765 for peginterferon plus ribavirin compared with best supportive care, resulting in an ICER of £903 per QALY gained.

4.2.9 The Assessment Group thought that the cost-effectiveness results were generally robust to variations in the limited number of parameters included in a deterministic sensitivity analysis reported in the manufacturer's submission. Probabilistic sensitivity analyses were also conducted by the manufacturer, and included the majority of parameters in the model. Although appropriate probability distributions appear to have been used for the probabilistic sensitivity analyses, the Assessment Group noted that limiting the distributions for some inputs does not appear to make the best use of data reported in the submission. Moreover, the Assessment Group felt that the manufacturer's model did not adequately consider logical relationships and potential correlations between model inputs. Rather than reporting the probability of cost effectiveness at certain willingness-to-pay thresholds, the submission identified a maximum threshold of £15,000 for all analyses. Further analyses of the manufacturer's model undertaken by the Assessment Group generally resulted in less favourable ICERs, but did not substantially alter the conclusions from those in the manufacturer's submission.

### **Schering-Plough**

4.2.10 The manufacturer presented cost-effectiveness results for three populations: people who had been treated previously with peginterferon and whose hepatitis C either did not respond to treatment or relapsed after treatment (broken down further by broad HCV genotype categories: genotypes 1 and 4 combined, and genotypes 2 and 3 combined) (data obtained from the EPIC3 clinical study

report); and people co-infected with HCV and HIV (using effectiveness data from a trial reported by Laguno and colleagues). The manufacturer subsequently presented an analysis of the cost effectiveness of shortened compared with standard treatment durations for people with HCV genotype 1.

- 4.2.11 Model-based economic evaluations were based on clinical data from the EPIC3 study (a multi-centre, non-randomised open-label uncontrolled study of re-treatment in people whose hepatitis C did not respond or relapsed after treatment) and from the study of Laguno and colleagues (a phase III open-label trial that recruited treatment-naïve [naïve to combination therapy] people with histologically verified liver disease, who were HIV-positive with controlled disease [for people with HCV and HIV co-infection]). As the included studies do not make the comparisons specified in the decision problem (that is, anti-viral treatment compared with best supportive care), the manufacturer assumed that people receiving best supportive care would not achieve a spontaneous sustained virological response. The model includes a low probability of a spontaneous sustained virological response for people with mild chronic hepatitis C, which is applied to the best supportive care and active treatment cohorts.
- 4.2.12 The manufacturer's model is structurally similar to that used in a previous assessment report for TA106. However, it does not distinguish between people achieving a sustained virological response from any of the treatment-eligible states (mild or moderate hepatitis C and compensated cirrhosis). The parameters reflecting natural history in the model are similar to those adopted in the previous assessment report (TA106), as are the health state utilities and health state costs (inflated from 2003/4 to 2007/8 costs using the HCHS Pay and Prices Index).
- 4.2.13 Re-treating people whose hepatitis C did not respond or relapsed following previous interferon treatment was estimated to result in a QALY gain of 1.03 compared with best supportive care at an incremental cost of £4536, resulting in an ICER of £4387 per QALY gained. These results were reported for a combined cohort of people with HCV genotypes 1 and 4 (84% of total) and people with genotypes 2 and 3. Separate results were also reported for the two genotype subgroups: the ICERs were £7177 per QALY gained for people with genotypes 1 and 4, and £783 per QALY gained for people with genotypes 2 and 3. Separate subgroup analyses (not stratified by genotype) for people whose

condition did not respond to treatment and for people whose condition relapsed following treatment were also presented which suggested that the QALY gain was higher for the non-response subgroup than for the relapse subgroup.

- 4.2.14 For a cohort of people (all HCV genotypes) co-infected with HCV and HIV, treatment with peginterferon plus ribavirin was estimated to result in a gain of 2.32 QALYs compared with best supportive care at an incremental cost of £2502, resulting in an ICER of £1077 per QALY gained. For people with genotypes 1 and 4 the ICER was estimated at £1637 per QALY gained, while for people with genotypes 2 and 3 the ICER was £403 per QALY gained.
- 4.2.15 The manufacturer also conducted an analysis of the subgroup of people eligible for a shortened treatment duration. The analysis demonstrated that a shortened treatment duration of 24 weeks dominated the standard treatment duration of 48 weeks for people with HCV genotype 1. The manufacturer noted that these results should be treated with caution, as there was a large numerical difference in the rapid virological response rates at week 4 between the patient groups (standard versus shortened treatment) in the clinical trial, despite the fact that they had received the same treatment up to this point.
- 4.2.16 Deterministic sensitivity analyses provided by the manufacturer showed that the ICERs for both the re-treated and co-infected groups were sensitive to variations in the early virological response rate and the sustained virological response rate, as well as to changes in body weight (since the dosing regimens of both peginterferon alfa-2b and ribavirin were weight-based). In the re-treatment group the ICERs showed a small increase in response to changes in the distribution of disease severity within the group.
- 4.2.17 Probabilistic sensitivity analyses were conducted by the manufacturer which included the majority of parameters in the model. The manufacturer performed probabilistic sensitivity analyses (for overall cohort and by genotype) for each group (re-treated and co-infected). The probabilistic sensitivity analysis indicated a high probability (over 90%) that treatment with peginterferon alfa-2b plus ribavirin is cost effective for all analyses at willingness-to-pay thresholds of both £20,000 and £30,000 per QALY gained.
- 4.2.18 The Assessment Group was concerned about the manufacturer's assumption

that a person would achieve a sustained virological response immediately after treatment is given, and therefore accrue health benefits before entering the model. Furthermore, the Assessment Group did not consider that it was appropriate to apply the same utility values for a sustained virological response irrespective of the stage of disease when the treatment was given. Further analyses of the manufacturer's model undertaken by the Assessment Group generally resulted in less favourable ICERs, but did not substantially alter the conclusions from those in the manufacturer's submission.

## Assessment Group's model

- 4.2.19 The Assessment Group adapted a previously published model to undertake an independent economic assessment of shortened treatment durations with peginterferon alfa plus ribavirin, using clinical-effectiveness data from studies included in the systematic review. The economic model was structurally similar to those developed by the manufacturers, and used similar input parameters to model disease progression, health state costs and utility. The model consists of nine health states representing stages of chronic liver disease and death.
- 4.2.20 The economic model contains three health states representing cure of chronic hepatitis C, which are differentiated by the stage of the disease before treatment, as this is expected to have an impact on the subsequent risk of progressive liver disease, post-treatment surveillance and health-related quality of life. The health states mild hepatitis C, moderate hepatitis C, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma and liver transplant represent stages of progressive liver disease. People not exhibiting a sustained virological response are expected to have the same risk of disease progression as untreated people. These assumptions are all consistent with previous assessments and with other published economic evaluations of anti-viral treatment for chronic HCV infection. The model has a cycle length of 1 year and incorporates a half-cycle adjustment.
- 4.2.21 Baseline population data in the model were based on the results of a clinical audit undertaken at a London teaching hospital. New patients were taken to represent the population of people with HCV and HIV co-infection and the population eligible to receive shortened courses of combination therapy as applicable, and existing patients were taken to represent the population of people treated previously with peginterferon alfa and ribavirin. Patients were

differentiated in terms of average age and distribution across stages of chronic liver disease (mild hepatitis C, moderate hepatitis C and compensated cirrhosis). The proportion of men in the baseline cohort was based on the Assessment Group's previous assessment. The majority of these assumptions do not affect response to treatment, but relate to the risk of all-cause mortality. The influence of the stage of chronic liver disease on response to treatment, and on the cost effectiveness of the intervention, was assessed in a sensitivity analysis.

- 4.2.22 Data on sustained virological response rates for the subgroup of people receiving shortened treatment courses were extracted by the Assessment Group from clinical trials included in the clinical effectiveness review. For the subgroups of people co-infected with HIV and HCV and of people whose hepatitis C did not respond to previous treatment or responded but subsequently relapsed, sustained virological response rates were taken from RCTs that included active comparators, which were not systematically reviewed by the Assessment Group. Data on sustained virological response rates were used in the model to estimate the probability of treatment-eligible people moving to the relevant state of a sustained virological response. Where applicable, early virological response rates were used to estimate the average duration of treatment and total drug acquisition costs for each anti-viral treatment strategy.
- 4.2.23 Shortening the duration of treatment with peginterferon alfa-2a plus ribavirin from 48 weeks to 24 weeks for people with HCV genotype 1, a baseline low viral load and a rapid virological response resulted in a reduction in total QALYs of between 0.08 and 0.14. This shortened treatment duration was also associated with a reduction in the total cost, resulting in ICERs that reflected 'savings per QALY lost' (ranging from £34,510 to £64,880 per QALY). For people with HCV genotypes 2 and 3, a baseline low viral load and a rapid virological response, a shortened duration of treatment of 16 weeks with peginterferon alfa-2a plus ribavirin dominated the standard 24-week treatment duration. For the subgroup of people with HCV genotype 1, a baseline low viral load and a rapid virological response, a shortened duration of treatment of 24 weeks with peginterferon alfa-2b plus ribavirin dominated the standard 48-week treatment duration.
- 4.2.24 The ICER for the subgroup of people who had been treated previously with peginterferon alfa-2b plus ribavirin or peginterferon monotherapy but whose

hepatitis C did not respond to treatment, or responded initially to treatment but subsequently relapsed, was £23,912 per QALY gained (compared with best supportive care) for people with HCV genotypes 1 and 4. If an early stopping rule was applied, the ICER for people with genotypes 1 and 4 was reduced to £7681 per QALY gained. For people with genotypes 2 and 3, treatment with peginterferon alfa-2b plus ribavirin dominated best supportive care (with or without an early stopping rule). Re-treatment with peginterferon alfa-2a plus ribavirin of people whose hepatitis C did not respond to previous peginterferon therapy resulted in an ICER of £52,587 per QALY gained for people with HCV genotype 1 and £10,926 per QALY gained for people with other genotypes, each compared with best supportive care. If an early stopping rule was applied at 12 weeks for people re-treated with peginterferon alfa-2a plus ribavirin who did not show an early virological response at this time, the ICERs were reduced to £9169 per QALY gained for people with HCV genotype 1 and £2294 per QALY gained for people with other genotypes.

- 4.2.25 For people co-infected with HCV and HIV, treatment with peginterferon alfa-2a plus ribavirin resulted in an ICER of £7941 per QALY gained for people with HCV genotypes 1 and 4 compared with best supportive care. Peginterferon alfa-2a plus ribavirin dominated best supportive care for people with genotypes 2 and 3. Treatment of people co-infected with HCV and HIV with peginterferon alfa-2b plus ribavirin resulted in an ICER of £11,806 per QALY gained for people with HCV genotypes 1 and 4 and an ICER of £2161 per QALY gained for people with genotypes 2 and 3.

## Summary of cost-effectiveness evidence

- 4.2.26 Cost-effectiveness analyses indicate that adopting a shortened duration of treatment with peginterferon alfa-2a plus ribavirin for people with HCV genotype 1 is associated with fewer QALYs, but also with lower treatment costs, resulting in ICERs ranging from £34,000 to £65,000 of savings per QALY lost. For people with genotypes 2 and 3, a shortened treatment course with peginterferon alfa-2a plus ribavirin dominates the standard treatment duration. Similarly, for people with HCV genotype 1, a shortened duration of treatment with peginterferon alfa-2b plus ribavirin dominates the standard treatment duration. The results submitted by the manufacturers and those reported by the Assessment Group also indicate that treatment with peginterferon alfa plus ribavirin for people who are eligible for re-treatment following previous non-



response or relapse of their condition is associated with QALY gains and an increase in costs. If an early stopping rule was applied at 12 weeks, re-treatment with peginterferon alfa plus ribavirin was associated with ICERs below £10,000 per QALY gained for people with HCV genotypes 1 and 4. For people with HCV genotypes 2 and 3, re-treatment was associated with ICERs below £2294 per QALY gained or dominated best supportive care. For people co-infected with HCV and HIV who were treated with peginterferon alfa plus ribavirin, either all ICERs were below £12,000 per QALY gained or treatment dominated best supportive care.

### 4.3 *Consideration of the evidence*

- 4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of peginterferon alfa (2a or 2b) plus ribavirin, having considered evidence on the nature of chronic hepatitis C and the value placed on the benefits of peginterferon alfa (2a or 2b) plus ribavirin by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.
- 4.3.2 The Committee was aware from the evidence presented that there were no statistically significant differences in sustained virological response rates between subgroups receiving shortened and standard courses of treatment with peginterferon alfa plus ribavirin. The Committee heard from the clinical specialist that, although some trials have reported that people who received shortened courses of treatment had (non-significant) lower sustained virological response rates, using shortened rather than standard courses of therapy was not expected to have clinical implications. Therefore the Committee concluded that shortened and standard treatment durations could be viewed as clinically comparable.
- 4.3.3 The Committee noted that no RCTs were identified that compared peginterferon alfa (with or without ribavirin) with best supportive care for people co-infected with HIV and HCV, or for people whose hepatitis C did not respond to previous treatment or responded but subsequently relapsed. The Committee heard from the clinical specialist that it would be unethical to conduct trials without an active comparator arm for these groups, and therefore the Committee should consider the use of sustained virological response rates from trials that had an active comparator to be appropriate for these subgroups.

The Committee agreed that using the results from trials that had an active comparator to derive data on clinical effectiveness for the economic model was appropriate.

- 4.3.4 The Committee discussed the assumption that people who receive best supportive care for chronic hepatitis C will not have a sustained virological response. The clinical specialist stated that sustained virological response rates are generally extremely low for people not receiving active therapy. The Committee concluded that it was therefore reasonable to assume that people who receive best supportive care do not achieve a sustained virological response.
- 4.3.5 The Committee heard from the patient experts that many people with chronic hepatitis C would be willing to tolerate the adverse effects of treatment with peginterferon alfa, with or without ribavirin, for the longest available treatment period to increase their chance of achieving a sustained virological response or to reduce the possibility of relapse following treatment, even if they knew that a shortened course of treatment may be associated with fewer adverse events. The Committee acknowledged that some people prefer to have a choice when considering their treatment options.
- 4.3.6 In response to comments received after consultation on the ACD, the Committee noted that the definition of undetectable serum HCV RNA (which denotes clearing of HCV) varied between the clinical trials (see section 4.1.3). They acknowledged that different laboratories in the UK use different tests and set different thresholds to determine whether a virus is undetectable, and that the quality of the test used may influence treatment decisions. The Committee therefore agreed that a highly sensitive test should be used to detect serum HCV RNA, to minimise the chance of false negative results – that is, to minimise the chance that the test indicates the absence of virus, leading erroneously to a shortened course of treatment, when in fact virus is present.
- 4.3.7 The Committee discussed the cost-effectiveness data presented by the manufacturers and the Assessment Group. The Committee noted that the Assessment Group adapted a previously published economic model, and that the model was structurally similar to those developed by the manufacturers, and used similar input parameters to model disease progression, health state costs and utility. The Committee noted that the model submitted by Roche

Products may have overestimated the QALY gains from achieving a sustained virological response, because the model did not differentiate between mild and moderate hepatitis C and because age-specific utilities were applied to the sustained virological response state but not to other health states. The Committee considered that it was not appropriate for the model to apply age-specific utility values to only one health state, but concluded that the additional analysis carried out by the Assessment Group to correct for this issue was appropriate.

- 4.3.8 The Committee was aware that the model from Schering-Plough for peginterferon alfa-2b assumed that a sustained virological response occurs at the beginning of a cycle rather than mid-cycle, and that the same utility values for a sustained virological response were used irrespective of the stage of disease when treatment starts. The Committee was satisfied that the additional analyses carried out by the Assessment Group corrected for these issues and did not substantially alter the results.
- 4.3.9 The Committee considered the cost effectiveness of peginterferon alfa and ribavirin combination therapy for the three populations covered by this appraisal. For people with HCV genotype 1, a baseline low viral load and a rapid virological response, the Committee noted that the shortened treatment duration of 24 weeks with peginterferon alfa-2a plus ribavirin was associated with a reduction in both QALYs and costs compared with the standard treatment duration of 48 weeks, resulting in ICERs that reflected 'savings per QALY lost' (ranging from £34,500 to £64,900 per QALY). The Committee considered situations where an ICER is derived from decreased effectiveness and decreased costs, and concluded that the commonly assumed decision rule of accepting ICERs below a given threshold is reversed, and so ICERs that are above the threshold are considered acceptable in this case. The Committee also noted that for people with genotype 1 who had a low viral load and a rapid virological response, the shortened treatment duration of 24 weeks with peginterferon alfa-2b plus ribavirin dominated the standard treatment duration of 48 weeks. Similarly, for people with HCV genotype 2 or 3, a baseline low viral load and a rapid virological response, the shortened treatment duration of 16 weeks with peginterferon alfa-2a plus ribavirin dominated the standard treatment duration of 24 weeks. Based on these ICERs, the Committee concluded that shortened courses of peginterferon alfa (2a or 2b) and ribavirin combination therapy represent a cost-effective use of NHS resources for people

eligible for this treatment regimen. The Committee noted that the cost effectiveness results also indicated that standard treatment durations were not likely to be considered cost effective compared with shortened treatment durations. Since the shortened and standard treatment durations are considered to be clinically comparable (see section 4.3.2), the Committee concluded that shortened treatment courses should be recommended rather than recommended as an option. However, the Committee was aware that shortened treatment courses are not suitable for all people. The Committee highlighted that when considering a shortened treatment course, clinicians should take into account the licensed indication of the chosen drug (peginterferon alfa-2a or peginterferon alfa-2b), the HCV genotype, the viral load at the start of treatment and the response to treatment (as indicated by the viral load).

4.3.10 The Committee then discussed whether peginterferon alfa (2a or 2b) plus ribavirin should be recommended for people who have been treated previously with peginterferon alfa (2a or 2b) and ribavirin in combination, or with peginterferon alfa monotherapy, and whose condition either did not respond to treatment or responded initially to treatment but subsequently relapsed. The Committee concluded that the analysis that incorporates an early stopping rule at 12 weeks for people who do not show an early virological response, as specified in the marketing authorisation, was the most appropriate scenario forming the basis of the cost-effectiveness analysis (see section 4.2.24). The Committee noted that the Assessment Group's analysis for people re-treated with peginterferon alfa plus ribavirin resulted in ICERs below £10,000 per QALY gained for people with HCV genotypes 1 and 4, and re-treatment dominated best supportive care for people with HCV genotypes 2 and 3. The Committee then considered the cost-effectiveness estimates for the subgroup of people with HIV and HCV co-infection. The Committee noted that in the Assessment Group's analysis for people co-infected with HCV and HIV who were receiving peginterferon alfa (2a or 2b) plus ribavirin, either all ICERs were below £12,000 per QALY gained or treatment dominated best supportive care. The Committee concluded that the ICERs presented in the base-case analysis by the Assessment Group were plausible for both the subgroup of people being re-treated and the subgroup of people co-infected with HCV and HIV. Based on these ICERs, the Committee was satisfied that peginterferon alfa (2a or 2b) and ribavirin combination therapy represents a cost-effective use of NHS resources both for people who have been treated previously and whose condition either

did not respond to treatment or responded initially to treatment but subsequently relapsed, and for people with HIV and HCV co-infection.

### Summary of Appraisal Committee's key conclusions

TA200 (MTA part review)	Appraisal title: Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C (part review of technology appraisal guidance 75 and 106)	Section
<b>Key conclusions</b>		
<p>Combination therapy with peginterferon alfa (2a or 2b) and ribavirin is recommended as a treatment option for adults with chronic hepatitis C:</p> <ul style="list-style-type: none"> <li>• who have been treated previously with peginterferon alfa (2a or 2b) and ribavirin in combination, or with peginterferon alfa monotherapy, and whose condition either did not respond to treatment or responded initially to treatment but subsequently relapsed or</li> <li>• who are co-infected with HIV.</li> </ul>		1.1
<p>Shortened courses of combination therapy with peginterferon alfa (2a or 2b) and ribavirin are recommended for the treatment of adults with chronic hepatitis C who:</p> <ul style="list-style-type: none"> <li>• have a rapid virological response to treatment at week 4 that is identified by a highly sensitive test and</li> <li>• are considered suitable for a shortened course of treatment.</li> </ul>		1.3
<b>Current practice</b>		
Clinical need of patients including the availability of alternative treatments	Clinical practice for the use of these technologies is described in NICE technology appraisal guidance 75 and 106. This appraisal addresses extensions to the marketing authorisations.	–
<b>The technology</b>		

<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>Not applicable (this is a review of established technologies).</p>	<p>–</p>
<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>This guidance updates and replaces:</p> <ul style="list-style-type: none"> <li>• section 1.2, bullet 3 only, of TA75</li> <li>• section 1.4 of TA75 for adults who are eligible for shortened courses of combination therapy (as described in section 1.2 of the current guidance)</li> <li>• section 1.7, bullet 1 only, of TA75</li> <li>• sections 1.4 and 1.5 of TA106.</li> </ul> <p>All other recommendations in TA75 and TA106 still stand.</p>	<p>–</p>
<p>Adverse effects</p>	<p>The Committee heard from the patient experts that many people with chronic hepatitis C would be willing to tolerate the adverse effects of treatment with peginterferon alfa, with or without ribavirin, for the longest available treatment period to increase their chance of achieving a sustained virological response or to reduce the possibility of relapse following treatment, even if they knew that a shortened course of treatment may be associated with fewer adverse events.</p>	<p>4.3.5</p>
<p><b>Evidence for clinical effectiveness</b></p>		

<p>Availability, nature and quality of evidence</p>	<p>RCT evidence was available for shortened treatment courses. No RCTs were identified that compared peginterferon alfa (with or without ribavirin) with best supportive care for people co-infected with HIV and HCV, or for people whose hepatitis C did not respond to previous treatment or responded but subsequently relapsed. The Committee agreed that it was appropriate to use results from trials that had an active comparator to derive data on clinical effectiveness for the economic model.</p>	<p>4.3.3</p>
<p>Relevance to general clinical practice in the NHS</p>	<p>The clinical specialist stated that sustained virological response rates are generally extremely low for people not receiving active therapy. The Committee concluded that it was therefore reasonable to assume that people who receive best supportive care do not achieve a sustained virological response.</p>	<p>4.3.4</p>
	<p>The Committee noted that the definition of undetectable serum HCV RNA (which denotes clearing of HCV) varied between the clinical trials, and therefore that the quality of the test used may influence treatment decisions. The Committee therefore agreed that a highly sensitive test should be used to detect serum HCV RNA, to minimise the chance of false negative results.</p>	<p>4.3.6</p>
<p>Uncertainties generated by the evidence</p>	<p>There were no major uncertainties generated by the evidence.</p>	<p>–</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>Not applicable.</p>	<p>–</p>

<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The Committee was aware from the evidence presented that there were no statistically significant differences in sustained virological response rates between subgroups receiving shortened and standard courses of treatment with peginterferon alfa plus ribavirin. The Committee heard from the clinical specialist that, although some trials have reported that people who received shortened courses of treatment had (non-significant) lower sustained virological response rates, using shortened rather than standard courses of therapy was not expected to have clinical implications. Therefore the Committee concluded that shortened and standard treatment durations could be viewed as clinically comparable.</p>	<p>4.3.2</p>
<p><b>Evidence for cost effectiveness</b></p>		
<p>Availability and nature of evidence</p>	<p>Cost effectiveness data were presented by the manufacturers and the Assessment Group.</p>	
	<p>The Committee noted that the Assessment Group adapted a previously published economic model, and that the model was structurally similar to those developed by the manufacturers, and used similar input parameters to model disease progression, health state costs and utility.</p>	<p>4.3.7</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>There were no material uncertainties around the assumptions and inputs in the economic models presented.</p>	<p>–</p>
	<p>The Committee noted that the model submitted by Roche Products may have overestimated the QALY gains from achieving a sustained virological response, because the model did not differentiate between mild and moderate hepatitis C and because age-specific utilities were applied to the sustained virological response state but not to other health states. The Committee considered that it was not appropriate for the model to apply age-specific utility values to only one health state, but concluded that the additional analysis carried out by the Assessment Group to correct for this issue was appropriate.</p>	<p>4.3.7</p>



	<p>The Committee was aware that the model from Schering-Plough for peginterferon alfa-2b assumed that a sustained virological response occurs at the beginning of a cycle rather than mid-cycle, and that the same utility values for a sustained virological response were used irrespective of the stage of disease when treatment starts. The Committee was satisfied that the additional analyses carried out by the Assessment Group corrected for these issues and did not substantially alter the results.</p>	4.3.8
<p>Incorporation of health-related quality of life benefits and utility values</p>		
<p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>No potential significant and substantial health-related benefits were identified that were not included in the economic models.</p>	-
<p>Are there specific groups of people for whom the technology is particularly cost-effective?</p>	<p>Not applicable.</p>	-

<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>For people with HCV genotype 1, a baseline low viral load and a rapid virological response, the Committee noted that the shortened treatment duration of 24 weeks with peginterferon alfa-2a plus ribavirin was associated with a reduction in both QALYs and costs compared with the standard treatment duration of 48 weeks, resulting in ICERs that reflected 'savings per QALY lost' (ranging from £34,500 to £64,900 per QALY).</p> <p>The Committee considered situations where an ICER is derived from decreased effectiveness and decreased costs, and concluded that the commonly assumed decision rule of accepting ICERs below a given threshold is reversed, and so ICERs that are above the threshold are considered acceptable in this case.</p> <p>The Committee also noted that for people with genotype 1 who had a low viral load and a rapid virological response, the shortened treatment duration of 24 weeks with peginterferon alfa-2b plus ribavirin dominated the standard treatment duration of 48 weeks. Similarly, for people with HCV genotype 2 or 3, a baseline low viral load and a rapid virological response, the shortened treatment duration of 16 weeks with peginterferon alfa-2a plus ribavirin dominated the standard treatment duration of 24 weeks.</p>	<p>4.3.9</p>
	<p>The Committee noted that the Assessment Group's analysis for people re-treated with peginterferon plus ribavirin resulted in ICERs below £10,000 per QALY gained for people with HCV genotypes 1 and 4, and re-treatment dominated best supportive care for people with HCV genotypes 2 and 3.</p> <p>The Committee noted that in the Assessment Group's analysis for people co-infected with HCV and HIV who were receiving peginterferon alfa (2a or 2b) plus ribavirin, either all ICERs were below £12,000 per QALY gained or treatment dominated best supportive care. The Committee concluded that the ICERs presented in the base-case analysis by the Assessment Group were plausible for both the subgroup of people being re-treated and the subgroup of people co-infected with HCV and HIV.</p>	<p>4.3.10</p>
<p><b>Additional factors taken into account</b></p>		

Patient access schemes (Pharmaceutical Price Regulation Scheme [PPRS])	None received.	-
End-of-life considerations	Not applicable to this appraisal.	-
Equalities considerations, social value judgements	No issues relating to equality were raised at any stage during the development of this appraisal.	-

## 5 Implementation

- 5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the [NICE website](#). When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.
- 5.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has chronic hepatitis C and the doctor responsible for their care thinks that peginterferon alfa and ribavirin is the right treatment, it should be available for use, in line with NICE's recommendations.
- 5.3 NICE has developed [tools](#) to help organisations put this guidance into practice (listed below).
- Costing report and costing template to estimate the savings and costs associated with implementation.
  - Audit support for monitoring local practice.

## 6 Related NICE guidance

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

## 7 Review of guidance

- 7.1 The guidance on these technologies will be considered for review by the Guidance Executive in July 2013. The Guidance Executive will decide whether the technologies should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon  
Chief Executive  
September 2010

## Appendix A: Appraisal Committee members and NICE project team

### *A Appraisal Committee members*

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

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

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

#### **Dr Amanda Adler (Chair)**

Consultant Physician, Addenbrooke's Hospital, Cambridge

#### **Professor Keith Abrams**

Professor of Medical Statistics, University of Leicester

#### **Dr Ray Armstrong**

Consultant Rheumatologist, Southampton General Hospital

#### **Dr Jeff Aronson**

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

#### **Dr Michael Boscoe**

Consultant Cardiothoracic Anaesthetist, Royal Brompton and Harefield NHS Foundation Trust

#### **Professor John Cairns**

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

**Dr Mark Chakravarty**

External Relations Director, Pharmaceuticals and Personal Health, Oral Care Europe

**Professor Jack Dowie**

Health Economist, London School of Hygiene and Tropical Medicine

**Dr Fergus Gleeson**

Consultant Radiologist, Churchill Hospital, Oxford

**Ms Sally Gooch**

Independent Nursing and Healthcare Consultant

**Mrs Eleanor Grey**

Lay member

**Dr Neil Iosson**

General Practitioner

**Dr Rosa Legood**

Lecturer, London School of Hygiene and Tropical Medicine

**Mr Terence Lewis**

Lay member

**Dr Ruairidh Milne**

Director of Strategy and Development and Director for Public Health Research, NIHR Evaluation, Trials and Studies Coordinating Centre, University of Southampton

**Dr Rubin Minhas**

General Practitioner and Clinical Director, BMJ Evidence Centre

**Mr Stephen Palmer**

Senior Research Fellow, Centre for Health Economics, University of York

**Dr John Pounsford**

Consultant Physician, Frenchay Hospital, Bristol

**Mr Philip Pugh**



Strategic Development Lead for Healthcare Associated Infection and Antimicrobial Resistance,  
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**Mr Cliff Snelling**

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**Professor Ken Stein (Vice Chair)**

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**Professor Andrew Stevens**

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

**Ms Nathalie Verin**

Health Economics Manager, Boston Scientific UK and Ireland

**Dr Colin Watts**

Consultant Neurosurgeon, Addenbrooke's Hospital, Cambridge

### ***B NICE project team***

Each technology appraisal is assigned to a team consisting of one or more health technology

analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Scott Goulden**

Technical Lead

**Fiona Rinaldi**

Technical Adviser

**Jeremy Powell**

Project Manager

## Appendix B: Sources of evidence considered by the Committee

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

- Hartwell D, Jones J, Baxter L, et al. Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation, December, 2009

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

I) Manufacturers/sponsors:

- Roche Products
- Schering-Plough (during the course of the appraisal, Schering-Plough merged with Merck Sharp & Dohme)

II) Professional/specialist and patient/carer groups:

- Association of Medical Microbiologists
- British Association for the Study of the Liver
- British Association for the Study of the Liver Nurses Forum
- British Infection Society
- British Liver Trust
- British Society of Gastroenterology
- British Viral Hepatitis Group
- Haemophilia Alliance
- Haemophilia Society
- Hepatitis C Trust

- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- South Asian Health Foundation

III) Other consultees:

- Department of Health
- Welsh Assembly Government

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

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Foundation for Liver Research
- MRC Clinical Trials Unit
- NHS Quality Improvement Scotland

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

- Professor Geoffrey Dusheiko, nominated by the Royal College of Physicians – clinical specialist
- Mr Charles Gore, nominated by the Hepatitis C Trust – patient expert
- Ms Raquel Jose, nominated by the Hepatitis C Trust – patient expert

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

- Roche Products
- Schering-Plough (during the course of the appraisal, Schering-Plough merged with Merck Sharp & Dohme)

## Changes after publication

**February 2014:** implementation section updated to clarify that peginterferon alfa and ribavirin is recommended as an option for treating chronic hepatitis C. Additional minor maintenance update also carried out.

**March 2012:** minor maintenance

## About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE [multiple technology appraisal](#) process.

This guidance should be read in conjunction with the following NICE guidance:

- NICE technology appraisal guidance 75 (TA75) '[Interferon alfa \(pegylated and non-pegylated\) and ribavirin for the treatment of chronic hepatitis C](#)' (which covers moderate to severe hepatitis C)
- NICE technology appraisal guidance 106 (TA106) '[Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C](#)'.

This appraisal addresses extensions to the marketing authorisations for peginterferon alfa-2a and peginterferon alfa-2b. This guidance updates and replaces:

- section 1.2, bullet 3 only, of TA75
- section 1.4 of TA75 for adults who are eligible for shortened courses of combination therapy (as described in section 1.2 of the current guidance)
- section 1.7, bullet 1 only, of TA75
- sections 1.4 and 1.5 of TA106.

All other recommendations in TA75 and TA106 still stand.

We have produced a [summary of this guidance for patients and carers](#). Tools to help you put the guidance into practice and information about the evidence it is based on are also [available](#).

### Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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### Accreditation

