

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Overview

### **Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of hepatitis C: Part-review of NICE technology appraisal guidance 106 and 75**

This document is a summary of the evidence and views submitted by consultees and the Assessment Group. It highlights key issues for discussion at the first Appraisal Committee meeting. NICE prepares the overview before it receives consultees' comments on the assessment report. The sources of evidence used in the preparation of this document are given in appendix A.

## Background

The purpose of this review is to determine the clinical effectiveness and cost effectiveness of peginterferon alfa (2a and 2b) in combination with ribavirin (or as monotherapy where ribavirin is contraindicated) for the treatment of chronic hepatitis C virus (HCV) in 3 specific subgroups:

- people eligible for shortened treatment courses
- people eligible for retreatment with peginterferon alfa (2a and 2b) plus ribavirin following previous non-response or relapse
- people who are co-infected with the human immunodeficiency virus (HIV)

Use of peginterferon alfa in these groups has been licensed since the publication of the previous NICE guidance on hepatitis C: 'Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C' (TA 75, 2004) and 'Peginterferon alfa and ribavirin for the treatment of mild hepatitis C' (TA 106, 2006). The relevant changes to the summaries of product characteristics for the peginterferons under review, including extensions to the licences is summarised as follows:

### **Peginterferon alfa-2a**

- Extension of the therapeutic indication to include treatment in people who previously did not respond to interferon (pegylated or non-pegylated) plus ribavirin. This includes people who had an early virological response but not an end-of-treatment sustained virological response ('relapse') and people who were treated but did not have a virological response ('non-response').
- Option to shorten the treatment duration in people with genotype 2 or 3 with low viral load at the start of treatment and a rapid virological response (defined as HCV RNA undetectable by week 4) from 24 weeks to 16 weeks.
- Option to shorten the treatment duration from 48 weeks to 24 weeks in people with genotype 1 with a low viral load and rapid virological response (defined as HCV RNA undetectable at week 4 and at week 24) and in people with genotype 4 and a rapid virological response.

The posology section has also been updated to include recommendations for people co-infected with HIV.

### **Peginterferon alfa-2b**

- Extension of the therapeutic indication of peginterferon alfa-2b plus ribavirin to include treatment in people who previously did not respond to interferon (pegylated or non-pegylated) plus ribavirin, or to interferon monotherapy.
- Extension of the therapeutic indication of peginterferon alfa-2b plus ribavirin to include treatment in people co-infected with the human immunodeficiency virus (HIV).

The posology section has also been updated regarding the lack of data to support the re-treatment of non-responding people with genotype 1 HCV for more than 48 weeks.

**Current guidance****NICE technology appraisal guidance 106 (2006)**

NICE issued guidance on the use of interferon alfa, pegylated interferon alfa (peginterferon alfa) and ribavirin in the treatment of people with moderate to severe chronic hepatitis C in January 2004 (NICE technology appraisal guidance 75; TA 75). The evidence in this appraisal relates to the extension of this treatment to people with mild chronic hepatitis C. For people with moderate or severe disease, the guidance in TA 75 still stands.

- 1.1 Combination therapy, comprising peginterferon alfa-2a and ribavirin or peginterferon alfa-2b and ribavirin, is recommended, within the licensed indications of these drugs, for the treatment of mild chronic hepatitis C.
- 1.2 Monotherapy with peginterferon alfa-2a or peginterferon alfa-2b is recommended, within the licensed indications of these drugs, for the treatment of mild chronic hepatitis C for people who are unable to tolerate ribavirin, or for whom ribavirin is contraindicated.
- 1.3 The decision on whether a person with mild chronic hepatitis C should be treated immediately or should wait until the disease has reached a moderate stage ('watchful waiting') should be made by the person after fully informed consultation with the responsible clinician. The decision to treat need not depend on a liver biopsy to determine the stage of the disease if treatment is initiated immediately. However, a biopsy may be recommended by the clinician for other reasons or if a strategy of watchful waiting is chosen.
- 1.4 The duration of treatment should vary according to the licensed indications of the chosen drug, the genotype of the virus, the initial viral load, the response to treatment, and the treatment regimen chosen.
- 1.5 Second or subsequent courses of treatment are not recommended for people who have been treated with a first course of either combination therapy or monotherapy with peginterferon alfa if they have not had an early response (as indicated by reduction in viral load at 12 weeks).
- 1.6 There is insufficient evidence to recommend combination therapy or monotherapy with peginterferon alfa for people with mild chronic hepatitis C who are under the age of 18 years, or those who have had a liver transplant.

**NICE technology appraisal guidance 75 (2004)**

- 1.1 Combination therapy with peginterferon alfa and ribavirin is recommended within its licensed indications for the treatment of people aged 18 years and over with moderate to severe chronic hepatitis C (CHC), defined as histological evidence of significant scarring (fibrosis) and/or significant necrotic inflammation.
- 1.2 People with moderate to severe CHC are suitable for treatment if they have:
  - not previously been treated with interferon alfa or peginterferon alfa, or
  - been treated previously with interferon alfa (as monotherapy or in combination therapy), and/or
  - previously received peginterferon alfa monotherapy only and responded at

the end of treatment but subsequently relapsed, or did not respond at the end of treatment.

- 1.3 People currently being treated with interferon alfa, either as combination therapy or monotherapy, may be switched to the corresponding therapy with peginterferon alfa.
- 1.4 Treatment for the groups identified in Sections 1.1 and 1.2 should be as follows.
- People infected with hepatitis C virus (HCV) of genotype 2 and/or 3 should be treated for 24 weeks.
  - For people infected with HCV of genotype 1, 4, 5 or 6, initial treatment should be for 12 weeks. Only people showing, at 12 weeks, a reduction in viral load to less than 1% of its level at the start of treatment (at least a 2-log reduction, see Section 4.1.2.5) should continue treatment until 48 weeks. For people in whom viral load at 12 weeks exceeds 1% of its level at the start of treatment, treatment should be discontinued.
  - People infected with more than one genotype that includes one or more of genotypes 1, 4, 5, or 6 should be treated as for genotype 1.
- 1.5 People satisfying the conditions in Sections 1.1 and 1.2 but for whom ribavirin is contraindicated or is not tolerated should be treated with peginterferon alfa monotherapy. Regardless of genotype, individuals should be tested for viral load at 12 weeks, and if the viral load has reduced to less than 1% of its level at the start of treatment, treatment should be continued for a total of 48 weeks. If viral load has not fallen to this extent, treatment should stop at 12 weeks.
- 1.6 People for whom liver biopsy poses a substantial risk (such as those with haemophilia, or those who have experienced an adverse event after undergoing a previous liver biopsy), and people with symptoms of extra-hepatic HCV infection sufficient to impair quality of life, may be treated on clinical grounds without prior histological classification.
- 1.7 There is insufficient evidence to recommend combination therapy using peginterferon alfa or interferon alfa in people who:
- have previously been treated with combination therapy using peginterferon alfa, and/or
  - are younger than 18 years of age, and/or
  - have had a liver transplantation. Treatment of CHC recurrence after liver transplantation (whether or not the person had been treated with interferon alfa or peginterferon alfa therapy at any time before transplantation) should be considered as experimental and carried out only in the context of a clinical trial.

## **1.1      *The condition***

Hepatitis C is a disease of the liver caused by the hepatitis C virus (HCV).

There are two main phases of infection: acute and chronic. Acute HCV refers to the period immediately after HCV infection, while chronic HCV is defined as infection persisting for more than 6 months. Generally the virus is transmitted parenterally through percutaneous exposure to contaminated blood, but the

natural history of the disease is not completely understood. In the UK, the most common source of HCV transmission is through injecting drug use, which accounts for approximately 90% of new cases. Other less common sources of infection include mother to baby transmission, occupational exposure (such as through a needle stick injury), tattooing and body piercing. Since the viral inactivation programme was implemented in the mid-1980s and blood donor screening started in 1991, the transmission of HCV in the UK via transfusion of blood, blood products or organ transplantation has all but ceased. Estimates from the Health Protection Agency suggest that approximately 142,000 people between the ages of 15 and 59 years were infected with chronic HCV in England and Wales in 2003; a prevalence of 0.44% in this age group. The prevalence of chronic HCV varies according to different populations, and is found to be more common in men and people aged 25 to 44 years.

Adults infected with HCV are often asymptomatic but about 20% will develop acute hepatitis; some of these people will experience non-specific symptoms including malaise, weakness and anorexia. Approximately 80% of those exposed fail to clear the virus and go on to develop chronic hepatitis. Chronic HCV is categorised as mild, moderate or severe depending on the extent of liver damage. The rate of progression of the disease is slow but variable, taking about 20–50 years from the time of infection. About 20–30% of those infected develop cirrhosis within 20 years, and a small percentage of these people are at high risk of hepatocellular carcinoma. A third may never progress to cirrhosis or will not progress for at least 50 years. Some people with end-stage liver disease or hepatocellular carcinoma may require liver transplantation.

The ability of people to rid themselves of HCV is related to the genotype of the virus, which affects the ability of the immune system to mount an effective response. Six major genotypes of HCV have been identified. In England and Wales, the most prevalent genotypes are 1 and 3, representing more than

90% of all diagnosed infection. Genotype 3a remains the most common, with a prevalence of 39%, followed by genotype 1a (22%).

It has been suggested that up to 10% of people with HCV are co-infected with HIV. Since the introduction of highly active antiretroviral therapy (HAART) in the mid to late 1990s, people with HIV infection are living longer and therefore those who are co-infected are becoming at risk of long-term HCV-related liver disease. It has been estimated that the time from HCV infection to cirrhosis is 23 years for people with HCV/HIV co-infection and 32 years for people with HCV alone. HCV/HIV co-infection is also associated with the fastest fibrosis progression, compared with other causes such as genetic haemochromatosis, primary biliary cirrhosis and alcoholic liver disease.

## **1.2 Current management**

The primary aim of treatment is to clear the virus from the blood. Successful treatment is usually indicated by a sustained virological response, defined as undetectable serum HCV RNA 6 months after treatment ends. A sustained virological response is generally considered to indicate permanent resolution of infection, although relapse may occur in approximately 5% of cases after 5 years.

Current NICE guidance (TA 75 and TA106) recommends combination therapy with ribavirin plus either peginterferon alfa-2a or peginterferon alfa-2b for adults with chronic HCV, regardless of disease severity. Monotherapy with peginterferon alfa-2a or peginterferon alfa-2b is recommended for people who are unable to tolerate ribavirin or for whom ribavirin is contraindicated. For those with mild HCV, the decision whether to treat immediately or adopt an approach of 'watchful waiting' is made by the patient and their clinician on an individual basis. Combination treatment with peginterferon alfa and ribavirin is currently restricted to people who are treatment naïve and who have previously been treated with non-peginterferon alfa combination therapy or monotherapy. It is also restricted to people who have previously been treated

with peginterferon alfa monotherapy but did not respond or subsequently relapsed.

It is estimated that only between 50 and 60% of people receiving anti-viral treatment have a sustained virological response. Current NICE guidance does not make provisions for people who have not responded to, or failed a previous course of peginterferon alfa and ribavirin combination therapy. In addition, there are no other licensed treatment options that could be used as second line therapies.

It is not thought that there are substantial variations in clinical practice across the country in terms of anti-viral treatment, although management of chronic HCV may vary according to the availability of hepatologists and specialist clinics. A substantial proportion of people seen in specialist clinics in England and Wales have had previous treatment and their condition has not responded or has relapsed. Definitions of prior non-response to treatment are increasingly important as different patterns of response may indicate the likelihood of an individual achieving a sustained virological response if re-treated with peginterferon alfa-2a or peginterferon alfa-2b plus ribavirin.

In recent years, one of the key aims of the management of HCV has been to maximise the likelihood of a sustained virological response while minimising potential adverse events of treatment, by using shorter treatment courses. Decisions regarding the most appropriate length of treatment may take into account the initial viral load, the genotype of the virus and early and rapid virological responses. Given the complexity of managing HCV and HIV co-infected adults, it is recommended that treatment is led by specialists in both HIV and HCV. The use of peginterferon alfa and ribavirin combination therapy is recommended in people with HCV/HIV co-infection, unless contraindicated. Treatment decisions for these individuals need to take into account possible drug interactions between HCV anti-viral treatment and HAART, such as significant HAART-associated hepatotoxicity.

## The technologies

**Table 1 Summary description of technologies**

Non-proprietary name	Pegylated interferon alfa-2a and ribavirin	Pegylated interferon alfa-2b and ribavirin
Proprietary name	Pegasys and Copegus	ViraferonPeg and Rebetol
Manufacturer	Roche Products	Schering-Plough
Dose		
Treatment naïve: genotypes 1 and 4	Peginterferon alfa-2a 180mcg once per week plus ribavirin for at least 24 weeks (low viral load $\leq$ 800,000 IU/ml at baseline; (not required for genotype 4) and an undetectable HCV RNA at weeks 4 to 24) or for 48 weeks (detectable HCV RNA at 4 weeks)	Peginterferon alfa-2b ( 1.5 mcg/kg bodyweight once per week plus ribavirin for at least 24 weeks if HCV RNA is detectable at week 24, or for 48 weeks if undetectable HCV RNA at week 12. For subset of people with low viral load ( $<$ 600,000 IU/ml) and HCV RNA negative at week 4 and remain negative at week 24, treatment may be given for 24 or 48 weeks (noting that patients may be at a higher risk or relapse after only 24 weeks of treatment)
Treatment naïve: genotypes 2 and 3	Peginterferon alfa-2a 180mcg once per week plus ribavirin for 16 weeks (low viral load $\leq$ 800,000 IU/ml and undetectable HCV RNA at weeks 4 to 16) or 24 weeks (detectable HCV RNA at 4 weeks)	Peginterferon alfa-2b 1.5 mcg/kg bodyweight once per week plus ribavirin for 24 weeks
Treatment naïve: genotypes 5 and 6	Data in this patient group is limited. Recommended treatment is peginterferon alfa-2a 180mcg once per week plus ribavirin (1000/1200mg dose) for 48 weeks	Patients infected with HCV of this type are usually managed as if they are infected with genotype 4 (Peginterferon alfa-2b 1.5 mcg/kg bodyweight once per week plus ribavirin for 48 weeks (HCV RNA below limits of detection at week 12)).
Treatment experienced: all genotypes	Peginterferon alfa-2a 180 mcg once per week plus ribavirin for 12 weeks (if detectable HCV RNA at week 12) or 48 weeks. If patients infected with HCV genotype 1 who do not respond to prior treatment with peginterferon alfa and ribavirin combination therapy are considered for re-treatment, the recommended total duration of therapy is 72 weeks	Peginterferon alfa-2b 1.5 mcg/kg bodyweight once per week plus ribavirin for 48 weeks (HCV RNA below limits of detection at week 12). Retreated people with no virological response at week 12 are unlikely to have a sustained virological response after 48 weeks of therapy
HIV/HCV co-infected: all genotypes	Peginterferon alfa-2a 180 mcg once per week monotherapy or	Peginterferon alfa-2b 1.5 mcg/kg bodyweight once per week plus



	in combination with ribavirin (800 mg) for 48 weeks	ribavirin for 48 weeks
Acquisition cost (BNF edition 58)	<p>Estimated total drug cost from assessment report.</p> <p>Dual treatment:</p> <ul style="list-style-type: none"> <li>• £4824 for 24 weeks</li> <li>• £11,425 for 48 weeks</li> <li>• £9647 for 48 weeks (HCV/HIV co-infected)</li> </ul> <p>Monotherapy:</p> <ul style="list-style-type: none"> <li>• £3046 for 24 weeks</li> <li>• £6092 for 48 weeks</li> </ul>	<p>Estimated total drug cost (based on 79 kg bodyweight) from assessment report.</p> <p>Dual treatment:</p> <ul style="list-style-type: none"> <li>• £5540 for 24 weeks (genotype 2/3)</li> <li>• £11,081 for 48 weeks (genotype 1)</li> </ul> <p>Monotherapy:</p> <ul style="list-style-type: none"> <li>• £3902 for 24 weeks</li> <li>• £7805 for 48 weeks</li> </ul>

The technologies assessed in this report are peginterferon alfa-2a and peginterferon alfa-2b plus ribavirin (or as monotherapy if ribavirin is contraindicated).

For both forms of peginterferon alfa, the therapeutic indication is the treatment of adults with chronic HCV who are positive for serum HCV RNA, including those with clinically stable HIV co-infection. The preferred indication is in combination with ribavirin, but monotherapy is indicated in cases of intolerance or contraindication to ribavirin. Patients may be treatment naïve or may have failed previous monotherapy or combination treatment.

The recommended dose of peginterferon alfa-2a (Pegasys, Roche Products) is 180 micrograms once per week, administered subcutaneously, for 16, 24, 48 or 72 weeks depending on genotype, baseline viral load, treatment response and prior therapies received (see Table 1). The recommended duration of peginterferon alfa-2a monotherapy is 48 weeks.

Peginterferon alfa-2b (ViraferonPeg, Schering-Plough) has a recommended dose of 1.5 mg/kg bodyweight once per week, administered subcutaneously for 24 or 48 weeks depending on genotype, baseline viral load, treatment response and prior therapies received (see Table 1).

Three forms of ribavirin (Rebetol (Schering-Plough), Copegus (Roche Products), and Ribavirin Teva (Teva UK)) are available which have recommended doses ranging from of 800 mg to 1400 mg depending on bodyweight, and are taken orally each day in two divided doses. . The dose of peginterferon alfa-2a also varies according to genotype: 800 mg per day for genotype 2 or 3 and 1000 to 1200 mg per day for genotypes 1, 4, 5 and 6 (1000 mg for bodyweight below 75 kg and 1200 mg for bodyweight 75 kg or more).

## **The evidence**

### **1.3 Clinical effectiveness**

Six randomised controlled trials (RCTs) reported in 8 publications were included in a systematic review of the available evidence for this appraisal. All of the included studies report peginterferon alfa and ribavirin combination therapy in people eligible for shortened courses of treatment. No studies were identified which compared peginterferon alfa (with or without ribavirin) to best supportive care for people with HIV/HCV co-infection or for those who did not previously respond to treatment or subsequently relapsed.

Four studies included peginterferon alfa-2a in combination with ribavirin, one trial evaluated peginterferon alfa-2b in combination with ribavirin, and one trial evaluated peginterferon alfa -2a or peginterferon alfa-2b in combination with ribavirin.

Shortened treatment for genotype 1 was evaluated in four trials, genotype 2 in one trial and genotypes 2 and 3 in one trial. Five of the trials included people with low viral load at baseline (based on mean viral load). The comparator in all included studies was the same intervention for a shorter duration. The dose of peginterferon alfa-2a was 180 mcg/week and the dose of peginterferon alfa-2b was 1.5 mcg/kg/week in all trials. All six RCTs reported sustained virological response as the primary outcome measure. This was defined as undetectable serum HCV RNA at the end of 24 weeks follow-up in four trials,

and as HCV-RNA-negative at the end of treatment and end of follow-up in two trials.

Four trials separately reported sustained virological response in the subgroup of patients who achieved a rapid virological response and had a low viral load at baseline, which is the patient subgroup which meets the licensed criteria for shortened courses of combination therapy.

In people with low viral load (800,000 IU/ml or less) who attained a rapid virological response, sustained virological response rates were comparable between groups who received 48 weeks (standard duration) of treatment (range 83% to 100%), and shortened treatment courses (range 84% to 96%), with no statistically significant differences between the groups. Sustained virological response rates were similar regardless of genotype with the exception of one trial (Berg et al. 2009), in which sustained virological responses were lower than in the other studies. This may have been because these rates are only for people who first became HCV RNA-negative at week 4, and do not include those who became HCV RNA-negative during weeks 1 to 3 (like the other studies). A summary of the outcomes in each trial, by genotype is shown in Table 2 below.

**Table 2 Sustained virological response by genotype**

Study details	Group 1	Group 2	p-value
<b>Genotype 1</b>			
Berg <i>et al.</i> 2009	PEG α-2b + RBV 48 weeks, n=225	PEG α-2b + RBV 24 weeks, n=28	
SVR by RVR, % (n/N)	42 (8/19)	57 (16/28)	p=not reported
Mangia <i>et al.</i> 2008	PEG α-2a or α-2b + RBV 48 wks, n=237	PEG α-2a or α-2b + RBV 24 wks, n=123	
SVR by RVR and baseline viral load, % (n/N):			
<400,000 IU/ml	83.3 (20/24)	84.4 (38/45)	p=0.83
≥400,000 IU/ml	86.8 (33/38)	73.1 (57/78)	p=0.14
Liu <i>et al.</i> 2008	PEG α-2a + RBV 48 wks, n=154	PEG α-2a + RBV 24 wks, n=154	p-value
SVR by RVR and baseline viral load, % (n):			

<400,000 IU/ml	100 (42)	94 (49)	$p=0.25$
<600,000 IU/ml	100 (50)	93 (61)	$p=0.13$
<800,000 IU/ml	100 (57)	94 (69)	$p=0.13$
<1,000,000 IU/ml	100 (61)	92 (71)	$p=0.03$
Yu <i>et al.</i> 2008	PEG $\alpha$ -2a + RBV 48 wks, n=100	PEG $\alpha$ -2a + RBV 24 wk, n=100	p-value
SVR by RVR and baseline viral load, % (n/N):			
<400,000 IU/ml (n=52)	100 (24/24)	96.4 (27/28)	$p=1.000$
$\geq$ 400,000 IU/ml (n=35)	100 (18/18)	76.5 (13/17)	$p=0.045$
<b>Genotype 2/3</b>			
Yu <i>et al.</i> 2007	PEG $\alpha$ -2a + RBV 24 wks, n=100	PEG $\alpha$ -2a + RBV 16 wks, n=50	p-value
SVR by RVR, % (n/N):			
RVR	98 (85/87)	100 (43/43)	$p=1$
no RVR	77 (10/13)	57 (4/7)	$p=0.610$
von Wagner <i>et al.</i> 2005	PEG $\alpha$ -2a + RBV 24 wks, RVR n=71	PEG $\alpha$ -2a + RBV 16 wks, RVR n=71	p-value
SVR by RVR and baseline viral load, % (n/N):			
$\leq$ 800,000 IU/ml (n=66)	87 (27/31)	94 (33/35)	$p=$ not reported
$>$ 800,000 IU/ml (n=75)	75 (30/40)	69 (24/35)	$p=$ not reported

PEG  $\alpha$ : peginterferon alfa; RBV: ribavirin

Two of the trials of peginterferon alfa-2a used doses of ribavirin according to body weight, which is no longer within the licensed indication. Both these trials restricted inclusion to people with genotype 2 or genotype 2 and 3. The marketing authorisation specifies that ribavirin should be given in fixed doses of 800 mg in people with genotype 2 or 3. Exclusion of the two trials on this basis would mean that there would be no evidence of the impact of shortened treatment durations in people with genotype 2 or 3.

Rapid virological response rates  $p$  were comparable for genotypes 1, 2 and 3, and there was no statistically significant difference between the groups that received the standard duration of treatment and those who received shortened courses. However, there was a large range in reported rapid virological response between the studies, with rates in people with genotype 2 or 3 generally being higher than in those with genotype 1.

The relapse rate in a subgroup of people with low viral load and a rapid virological response was reported in one trial (Yu et al. 2008). Relapse was defined as the re-appearance of serum HCV RNA during the 24 week follow up period in patients who had an initial response to treatment. The rates of relapse were low and were not statistically significantly different between the treatment arms (3.6% for 24 weeks versus 0% for 48 weeks,  $p=1.00$ ). In people with a rapid virological response and a high viral load, shortening the duration of treatment resulted in higher rates of relapse, reaching statistical significance (23.5% for 24 weeks versus 0% for 48 weeks,  $p=0.045$ ).

Adverse events were presented for treatment groups as a whole, and not for the subgroup of people with low viral load who had a rapid virological response. All but one trial reported the frequency of specific adverse events. Overall, the frequency of adverse events was not statistically different between treatment arms, although a lower incidence of adverse events was reported in three trials in people treated for a shorter duration. The most frequently occurring adverse events included flu-like symptoms, insomnia, anorexia, dermatological symptoms and alopecia.

The incidence of dose discontinuations was significantly lower in those receiving a shortened treatment regimen in one trial (10% versus 3%,  $p=0.045$ ).

The incidence of serious adverse events was low (range 0% to 7%), as reported in five trials. Frequencies of serious adverse events were not different between treatment arms although levels of statistical significance were lacking in most studies. Only one death was reported which was due to reactivation of pulmonary tuberculosis in a patient with a pre-existing condition.

## **Summary**

The collective evidence for combination therapy for both peginterferon alfa-2a and peginterferon alfa-2b, suggests that people with HCV may be treated with

a shorter course of peginterferon alfa plus ribavirin combination therapy for 16 weeks (genotype 2 or 3), or 24 weeks (genotype 1), without comprising sustained virological response rates. However, the assessment report notes that analyses of the sustained virological responses achieved according to baseline low viral load and rapid virological response are likely to be underpowered because they were based on randomised subgroups of varying sizes and therefore the results should be interpreted with caution.

## **1.4 Cost effectiveness**

### **Studies from the literature**

The searches conducted by the Assessment Group did not identify any studies assessing the cost-effectiveness of shortened courses of treatment, or of re-treating people who had not responded to previous therapy or who had relapsed. However, two studies (Kuehne et al. 2002; Campos et al. 2007) in people co-infected with HCV/HIV were identified. The studies compared peginterferon alfa and 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.

In the study by Kuehne et al. both peginterferon alfa monotherapy and peginterferon alfa plus ribavirin dominated the other strategies in patients with genotype 1 (mild and moderate HCV). Peginterferon alfa monotherapy was the more cost-effective option in each scenario. In patients with other genotypes (not genotype 1), peginterferon alfa and ribavirin combination therapy was the least cost-effective option (\$300,800 to \$4,000,000 per QALY gained for 48 weeks of treatment in patients with CD4 cell counts of 350 cells/ $\mu$ l and 200 cells/ $\mu$ l respectively). Monotherapies dominated in each case.

In the study by Campos et al. Peginterferon alfa in combination with ribavirin was the dominant treatment strategy (all treatments assumed to be administered for 48 weeks). Results suggested that the incremental cost per life year saved (LYS) of peginterferon with ribavirin in patients with genotypes

other than 1, was approximately half (\$39,300/LYS in women and \$39,700/LYS in men) that of the incremental cost in patients with genotype 1 (\$70,000/LYS in women and \$73,000/LYS in men).

The Assessment Group noted that both evaluations were conducted in the context of the US healthcare system and should be viewed with caution because of the mixed methodological quality of the included studies.

### **Manufacturers' submissions**

The Assessment Group reported that the manufacturers' economic models were structurally similar, but not identical, to that adopted for the previous assessment report for NICE (for TA106) and that they generally used similar natural history parameters, health state utilities and health state costs. The structural differences and the differences in parameter inputs between the manufacturers' models were considered likely to over-estimate the utility gain from treatment. The Assessment Group undertook additional analyses to quantify the impact of these differences on the QALY gains from treatment and on the resulting ICER. A summary of each model (from the manufacturers and the Assessment Group) is provided below.

### **Roche Products**

A health state transition model was submitted by Roche Products which was used to assess the cost-effectiveness of treatment with peginterferon alfa-2a in three groups:

- People who had been previously treated with peginterferon alfa, including those who did not respond to previous treatment (by genotype) and those who relapsed on previous treatment
- People with low viral load and rapid virological response who receive shortened courses of treatment with peginterferon alfa (by genotype)
- People co-infected with HCV/HIV

The model used clinical-effectiveness data from published RCTs, although effectiveness evidence for shortened treatment duration was derived from sub-group analyses. A number of the clinical-effectiveness studies included used by the manufacturer (namely patients who did not respond or relapsed and patients with HCV/HIV co-infection) had active comparators, rather than best supportive care (as outlined in the decision problem). In the majority of situations the comparison with supportive care assumed that the spontaneous sustained virological response rate will be zero, which generally accords with clinical opinion. There is no discussion or critical analysis of the reliability or generalisability of the clinical-effectiveness evidence used to populate the model.

Shortening the duration of treatment results in a QALY loss compared with standard treatment duration, as a result of a slight reduction in sustained virological reponse, as well as a reduction in costs. Since both costs and outcomes are lower with shortened treatment duration, the ICERs are positive (in the south-east quadrant of the cost-effectiveness plane) and were £15,472 per QALY gained for genotype 1 and 4 patients and £2,719 per QALY gained for genotype 2 & 3 patients (Table 3).

**Table 3 Base case results from Roche cost-effectiveness analysis**

Patient group	Genotype	Treatment	Cost (£)	QALYs	ICER (£ per QALY gained)
Non-responders	1	No treatment	27,114	11.06	3,334
		PEG 2a+RBV <sup>a</sup>	29,224	11.69	
	Non-1	No treatment	27,114	11.06	809
		PEG 2a+RBV <sup>b</sup>	27,942	12.08	
Relapsed on previous treatment	All	No treatment	27,114	11.06	Dominant
		PEG 2a+RBV	21,199	13.74	
Shortened treatment duration for patients with LVL and RVR	1 + 4	PEG 2a+RBV 48 wks	13,387	15.78	15,472
		PEG 2a+RBV 24 wks	8,866	15.49	
	2 + 3	PEG 2a+RBV 24	8,053	15.64	2,719



		wks			
		PEG 2a+RBV 16 wks	7,391	15.39	
HCV/HIV co-infected patients	All	IFN 2a+RBV	32,431	11.62	Dominant
		PEG 2a+RBV	28,786	12.99	

PEG 2a: peginterferon alfa-2a; RBV: ribavirin; LVL: low viral load; RVR: rapid virological response; IFN: non-pegylated interferon

<sup>a</sup>72 weeks treatment for patients showing an early virological response, 12 weeks treatment for patients not showing an early virological response; <sup>b</sup>48 weeks treatment for patients showing an early virological response, 12 weeks treatment for patients not showing an early virological response.

Re-treating people who relapsed following previous peginterferon treatment was reported as dominating supportive care (Table 3). This arises from a high sustained virological response observed in one trial that may not be generalisable to other populations of relapsed patients. The majority of patients in the study were genotype 1 patients who had received a shorter duration of treatment than the current standard of care (24 weeks rather than 48 weeks). The sustained virological responses applied in the model for re-treatment of patients who did not respond to previous peginterferon treatment were lower than for relapsed patients. While treatment resulted in QALY gains compared with best supportive care, the estimated reduction in costs of managing progressive liver disease did not fully offset treatment costs, resulting in positive ICERs (in the north-west quadrant of the cost-effectiveness plane) of £3,334 for genotype 1 patients and £809 for genotype non-1 patients (Table 3). The majority of patients recruited to the trial of non-responders to previous peginterferon treatment were genotype 1. There were only 29 genotype non-1 patients (9% of the arm used to estimate effectiveness of treatment in the model) the majority (66%) of which were genotype 4.

For people with HCV/HIV co-infection, treatment with peginterferon was estimated to dominate 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 patients would be zero and estimated a QALY gain (using the manufacturer's model) of 1.95 and an incremental cost of £1,765, for peginterferon compared with best supportive care, resulting in an ICER of £903 per QALY gained.

The cost-effectiveness results were considered to be generally robust to variation in a limited number of parameters included in a deterministic sensitivity analysis reported in the manufacturer's submission. Probabilistic sensitivity analyses (PSA) were conducted, and included the majority of parameters in the model. While appropriate distributions appear to have been used for the PSA, the parameterisation of the distributions for some inputs does not appear to make best use of data reported in the submission. Moreover there seems to have been a lack of consideration regarding logical relationships and potential correlation between model inputs. Rather than report 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 the manufacturer's submission.

### **Summary of general issues relating to the economic model identified by the Assessment Group**

- The manufacturer's model appears likely to overestimate the QALY gain from achieving a sustained virological response by:
  - applying age-specific utilities to the sustained virological response state and not applying age-specific utilities to other health states.
  - collapsing the HCV state into one, rather than differentiating mild and moderate HCV (which appear to have different health state values)
- The model assumes that all patients start treatment in the moderate HCV state. It is likely that some patients will present at other stages of liver

disease, including compensated cirrhosis. The base case results, applying to patients with moderate liver disease, may not apply to this group.

- The manufacturer's model does not include the cost of the health state patients are in when they start treatment.
- The cost applied for surveillance of patients who achieve a sustained virological response is low compared to that estimated in the UK Mild Hepatitis C Trial. This cost is only applied for the year following transition to the sustained virological response state
- The manufacturer's model appears to be applying an incorrect cost for ribavirin (for genotype 2/3 patients and for the HCV/HIV co-infected group).
- The parameterisation of some distributions in the PSA is based on assumed values and could be improved on. Additionally, some logically-related parameters appear to be sampled independently in the PSA, which is likely to give misleading results.

### **Schering-Plough**

The manufacturer presented cost-effectiveness results for two populations:

- People who have previously been treated with peginterferon and who did not respond to previous treatment or who relapsed on previous treatment (broken down by broad genotype categories: genotypes 1 and 4 combined, or genotypes 2 and 3 combined) (data obtained from the EPIC3 clinical study report).
- People co-infected with HCV/HIV (using effectiveness data from the Laguno and colleagues trial).

No assessment was presented on the cost-effectiveness of shortened versus standard treatment duration.

The submission included model-based economic evaluations based on clinical data from a multi-centre, non-randomised open label uncontrolled study (for

re-treatment in non-responding or relapsing patients) and a phase III open-label trial (for patients with HCV/HIV co-infection). As the included studies do not make the comparisons specified in the decision problem (anti-viral treatment compared with best supportive care) the manufacturer has assumed that the spontaneous sustained virological response rate for moderate chronic HCV and compensated cirrhosis (applied to best supportive care patients) will be zero, which is generally accord with clinical opinion. The model includes a low spontaneous sustained virological response probability for patients with mild chronic HCV, which is applied to patients in the best supportive care and active treatment cohorts.

The manufacturer's model is structurally similar to that used in the previous assessment report for NICE (TA106). However it does not distinguish between patients achieving a sustained virological response from any of the treatment-eligible states (mild or moderate HCV and compensated cirrhosis). Utility estimates published from the UK Mild Hepatitis C trial would suggest that these states should be separate. The natural history parameters in the model are similar to those adopted in the previous assessment report for NICE (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).

No systematic searches for health state utilities or costs are reported. The manufacturers did not report a critical appraisal of the EPIC3, Scotto and colleagues or Laguno and colleagues 2004 trials, which provided the clinical-effectiveness data for the model and sensitivity analyses. It is therefore difficult to judge the reliability or generalisability of the data used to populate the model. Costs and health state utilities were primarily derived from the Mild Hepatitis C trial.

Re-treating patients who did not respond or relapsed following previous interferon treatment was estimated to result in a QALY gain of 1.03, compared with supportive care, at an incremental cost of £4,536, resulting in an ICER of

£4,387 per QALY gained (Table 4). These results were reported for a combined cohort of genotypes 1 and 4 (84% of total) and genotypes 2 and 3 patients. Separate results are also reported for the two genotype sub-groups: the ICERs were £7,177 per QALY gained for people with genotypes 1 and 4 and £783 per QALY gained for those with genotypes 2 and 3.

**Table 4 Base case results from Schering-Plough economic evaluation**

Patient group	Genotype	Treatment	Cost (£)	QALYs	ICER (£ per QALY gained)
Non-responders / relapsers	1 + 4	No treatment	22,130	9.97	7,177
		PEG 2b+RBV	27,125	10.67	
	2 + 3	No treatment	22,130	9.97	783
		PEG 2b+RBV	24,301	12.75	
	All	No treatment	22,130	9.97	4,387
		PEG 2b+RBV	26,666	11.01	
HCV/HIV co-infection	1 + 4	No treatment	24,494	10.90	1,637
		PEG 2b+RBV	27,790	12.91	
	2 + 3	No treatment	24,494	10.90	403
		PEG 2b+RBV	25,645	13.75	
	All	No treatment	24,494	10.90	1,077
		PEG 2b+RBV	26,997	13.22	

PEG 2b: peginterferon alfa-2b; RBV: ribavirin

The submission also reports sub-group analyses (not stratified by genotype) for non-responding and relapsed patients separately which suggest that the QALY gain is higher for relapsed than for non-responding patients.

Effectiveness data for this group of patients was taken from the unpublished EPIC study, which recruited patients who had been previously treated with non-peginterferon as well as peginterferon. The effectiveness data in the model appear not strictly to meet the scope issued by NICE, as they appear to be based on all patients in the EPIC study, not just those who were previously treated with peginterferon.

For a cohort of patients (of all genotypes) co-infected with HCV/HIV, treatment with peginterferon was estimated to result in a gain of 2.32 QALYs compared

with no treatment, at an incremental cost of £2,502, resulting in an ICER of £1,077 per QALY gained. For patients with genotypes 1 and 4 the ICER was estimated at £1,637 per QALY gained, while for patients with genotypes 2 and 3 the ICER was £403 per QALY gained (Table 4).

The deterministic sensitivity analysis showed that the ICERs for both the re-treated and co-infected cohorts were sensitive to variation in the early virological response and sustained virological response rates, and to changes in patient weight since dosing of both peginterferon alfa-2b and ribavirin are weight-based. In the re-treatment group ICERs showed a small increase in response to changes in disease severity distribution within the patient group.

Probabilistic sensitivity analyses were conducted which included the majority of parameters in the model. The choice of distribution applied to parameters appears to have been appropriate. Three PSAs are reported for each patient group (re-treated and HCV/HIV co-infected patients). The first is for the overall cohort of patients followed by separate analyses for genotype sub-groups. The PSA reports high probability (over 90%) of treatment with peginterferon alfa-2b being cost effective for all analyses, at a willingness to pay threshold of £20,000 and £30,000.

### **Summary of general issues relating to the economic model identified by the Assessment Group**

- The Schering-Plough model appears to under-estimate the sustained virological response rate in each analysis, as a result of applying an unnecessary adjustment for treatment discontinuation, but appears to over-estimate the utility gain through treatment by not applying an adjustment for treatment discontinuation
- There is an implicit assumption that patients achieve a sustained virological response immediately after treatment is initiated and therefore accrue health benefits on entering the model. The Assessment Group indicated that it might be more reasonable to

assume that transitions occur mid-cycle (essentially applying half-cycle adjustment). This would mean adjusting cycle lengths (currently annual) to cope with treatments that are significantly less than 52 weeks, or calculating a weighted combination of the utility for the initial state and the utility for the appropriate sustained virological response state (weighted according to what proportion of the cycle is spent in the initial health state and what proportion in the sustained virological response state).

- The model collapses the sustained virological response state into one and therefore does not track whether patients have achieved a sustained virological response from mild HCV, moderate HCV or compensated cirrhosis. It applies the same health state utility to patients achieving a sustained virological response, irrespective of their stage of liver disease when treatment was initiated. This doesn't accord with utility data from the UK Mild Hepatitis C trial which reported a lower mean utility for patients achieving a sustained virological response from moderate liver disease than those achieving sustained virological response from mild liver disease;
- The model assumes that the sustained virological response health state cost is applied for all cycles the patient remains in the sustained virological response state. This differs from the assumption applied in the previous appraisal (TA106) where it was assumed that the sustained virological response cost applied only for the year following treatment response.
- The model appears to have underestimated the cost of ribavirin. The weekly cost of ribavirin is reported as £16.41 for re-treated patients and £13.13 for HCV/HIV co-infected patients. These are derived using an estimated average cost per 200mg tablet of ribavirin of approximately £3.28. However the figures used in the manufacturer's submission are the daily, not weekly costs.

**Assessment report**

The Assessment Group adapted a previously published model to undertake an independent economic assessment of shortened treatment duration with peginterferon alfa, using clinical-effectiveness data included in their 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 non-absorbing health states representing stages of chronic liver disease and one absorbing state representing death.

The economic model contains three health states representing cure of chronic HCV, which are differentiated by the patient's stage of disease (mild HCV, moderate HCV and compensated cirrhosis) prior to treatment as these are expected to have an impact on subsequent risk of progressive liver disease, post-treatment surveillance and also health-related quality of life (HRQoL). The remaining six, non-absorbing, states (mild HCV, moderate HCV, compensated and decompensated cirrhosis, hepatocellular carcinoma and liver transplant) represent stages of progressive liver disease. Patients not exhibiting a sustained virological response are expected to face the same risk of disease progression as untreated patients. These assumptions are all consistent with previous assessments, and other published economic evaluations of anti-viral treatment for chronic HCV. The model has a cycle length of one year and incorporates a half-cycle adjustment.

Baseline populations in the model were based on a clinical audit undertaken at a London teaching hospital. These differentiated between new and existing patients in terms of average age and the distribution of patients across stages of chronic liver disease (mild HCV, moderate HCV and compensated cirrhosis). The proportion of men in the baseline cohort was based on our previous assessment. The majority of these assumptions do not affect response to treatment, but relate to patients' risk of all-cause mortality. The influence of stage of chronic liver disease on response to treatment (and the



effect on cost-effectiveness of intervention) was assessed in a sensitivity analysis.

Sustained virological response rates extracted from clinical trials included in the clinical-effectiveness review were used in the model to estimate the probability of treatment-eligible patients transitioning to a relevant sustained virological response state. Where applicable, early virological responses were used to estimate the average duration of treatment and total drug acquisition costs for each anti-viral treatment strategy. Early stopping of treatment in patients unlikely to achieve a sustained virological response can have a significant impact on the cost-effectiveness of treatment with peginterferon alfa.

**Shortened treatment**

The clinical effectiveness review undertaken by the Assessment Group included five trials of shortened treatment duration used in the economic evaluation. Shorter duration of treatment with peginterferon alfa-2a (from 48 weeks to 24 weeks) for people with genotype 1 with baseline low viral load and who have a rapid virological response reduced total costs by approximately one-third, but was also associated with slightly poorer outcome. The resulting ICERs ranged from £34,510 to £64,880 per QALY gained (Table 5).

**Table 5 Base case cost-effectiveness for shortened treatment duration using peginterferon alfa-2a and ribavirin combination therapy in genotype 1 patients**

RCT		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per QALY gained)
Liu <i>et al.</i>	Standard (48 wks)	14,206	20.86	15.68	
	Shortened (24 wks)	9,399	20.76	15.54	
	Incremental	-4,807	-0.11	-0.14	34,510
Yu <i>et al.</i> 2008	Standard (48 wks)	14,206	20.86	15.68	
	Shortened (24 wks)	8,994	20.80	15.60	
	Incremental	-5,212	-0.07	-0.08	64,880

For people with genotypes 2 and 3 and low baseline viral load and who have a rapid virological response, shorter duration of treatment (16 weeks) with peginterferon alfa-2a dominated the standard 24-week treatment duration (Table 6).

**Table 6 Base case cost-effectiveness for shortened treatment duration using peginterferon alfa-2a and ribavirin combination therapy in genotype 2 or 3 patients**

RCT		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per QALY gained)
Yu <i>et al.</i> 2007	Standard (24 weeks)	7,834	20.82	15.64	
	Shortened (16 wks)	5,728	20.86	15.72	
	Incremental	-2,107	0.04	0.08	Shortened duration dominates
von Wagner <i>et al.</i>	Standard (24 weeks)	10,089	20.61	15.31	
	Shortened (16 wks)	6,943	20.75	15.54	
	Incremental	-3,146	0.14	0.23	Shortened duration dominates

For the subgroup of people with genotype 1 with baseline low viral load and who have a rapid virological response, shorter duration of treatment (24 weeks) with peginterferon alfa-2b dominated the standard 48-week treatment duration.

### Re-treatment

The assessment report did not identify any relevant randomised control trials of the re-treatment of people following previous non-response or relapse. Therefore data that has not been formally quality-assessed in the same way as for the review of shortened treatment duration has been used in the analysis for this subgroup of people.

Re-treatment with peginterferon alfa-2a of people who did not respond to previous peginterferon therapy resulted in an ICER of £52,587 per QALY

gained for people with genotype 1 and £10,926 per QALY gained for people with other genotypes (Table 7).

**Table 7 Base case cost-effectiveness for re-treatment using peginterferon alfa-2a and ribavirin combination therapy in previously treated patients**

Genotype		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per QALY gained)
Genotype 1	BSC	26,221	16.75	10.74	52,587
	Peg α-2a	42,350	17.07	11.05	
	Incremental	16,130	0.33	0.31	
Genotype non-1	BSC	26,221	16.75	10.74	10,926
	Peg α-2a	32,640	17.28	11.33	
	Incremental	6,419	0.54	0.59	

BSC: best supportive care; Peg α-2a: peginterferon alfa-2a

If an early stopping rule was applied at 12 weeks to re-treated people who did not have an early virological response, the ICERs reduced to £9169 per QALY gained for people with genotype 1 and £2294 per QALY gained for people with other genotypes (Table 8).

**Table 8 Cost-effectiveness of re-treatment using peginterferon alfa-2a and ribavirin combination therapy in previously treated patients – applying early stopping rule for patients not demonstrating an early virological response**

Genotype		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per QALY gained)
Genotype 1	BSC	26,221	16.75	10.74	9,169
	Peg α-2a	29,619	17.07	11.11	
	Incremental	3,398	0.33	0.37	
Genotype non-1	BSC	26,221	16.75	10.74	2,294
	Peg α-2a	27,636	17.28	11.36	
	Incremental	1,415	0.54	0.62	

BSC: best supportive care; Peg α-2a: peginterferon alfa-2a

Sustained virological responses for the subgroup of re-treated people receiving peginterferon alfa-2b were taken from the Schering-Plough report.

The ICER for re-treatment of people with genotypes 1 and 4 was £23,912 per QALY gained and the re-treatment for genotypes 2 and 3 resulted in peginterferon alfa-2b dominating best supportive care. If an early stopping rule was applied, the ICER for people with genotypes 1 and 4 reduced to £7681 per QALY gained. For people with genotypes 2 and 3 the incremental costs were reduced further, to -£2850, and the QALYs gained increased slightly.

**HIV/HCV co-infection**

As with the subgroup of re-treated people, no relevant randomised control trials were identified for the subgroup of HIV/HCV co-infected people, resulting in the inclusion in to the economic model of data that has not been formally quality-assessed.

For people co-infected with HCV/HIV, treatment with peginterferon alfa-2a resulted in an ICER of £7941 per QALY gained for people with genotypes 1 and 4, and peginterferon alfa-2a dominating best supportive care for people with genotypes 1 and 4 (Table 9).

**Table 9 Base case cost-effectiveness for treatment of HCV/HIV co-infected patients with peginterferon alfa-2a and ribavirin combination therapy**

Genotype		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per QALY gained)
Genotypes 1 + 4	BSC	22,201	18.93	12.65	
	Peg α-2a	28,133	19.43	13.40	
	Incremental	5,932	0.51	0.75	
Genotypes 2 + 3	BSC	22,201	18.93	12.65	
	Peg α-2a	20,484	20.13	14.51	
	Incremental	-1,717	1.20	1.86	

BSC: best supportive care; Peg α-2a: peginterferon alfa-2a

For people co-infected with HCV/HIV, treatment with peginterferon alfa-2b resulted in an ICER of £11,806 per QALY gained for genotypes 1 and 4, and £2161 per QALY gained for genotypes 2 and 3 (Table 10).

**Table 10 Base case cost-effectiveness for treatment of HCV/HIV co-infected patients with peginterferon alfa-2b and ribavirin combination therapy**

Genotype		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per QALY gained)
Genotypes 1 + 4	BSC	22,201	18.93	12.65	
	Peg $\alpha$ -2b	30,102	19.38	13.32	
	Incremental	7,901	0.46	0.67	11,806
Genotypes 2 + 3	BSC	22,201	18.93	12.65	
	Peg $\alpha$ -2b	25,190	19.83	14.03	
	Incremental	2,989	0.91	1.38	2,161

BSC: best supportive care; Peg  $\alpha$ -2b: peginterferon alfa-2b

### Summary of general concerns relating to the Assessment Group's model

- The majority of the clinical trials used to model response to treatment (sustained virological response and, where relevant, early virological response) were not included in the Assessment Group's systematic review, and have not been fully critically appraised. Only clinical trials relating to shortened treatment duration were included. In the case of re-treated patients and those with HCV/HIV co-infection, no trials were found that met the scope for this appraisal (of having placebo or supportive care control arms). As a result, the model uses clinical trial data that have not been assessed for risk of bias. The effectiveness data for patients with HCV/HIV co-infection have been extracted from published systematic reviews/meta analyses and, while these were quality assessed during the process of the published reviews, they have not been quality assessed or critically assessed for the assessment report.
- Some of the effectiveness data included in the model has been taken from comparatively small trials (20 to 40 patients per arm) that were not adequately powered to detect differences in sustained virological response, or were derived from sub-groups of patients in larger trials. In some cases the reporting of outcomes has not been consistent; for example, von Wagner and colleagues report sustained virological

response rates for patients with rapid virological response and low viral load while Yu and colleagues report sustained virological responses for patients with rapid virological response but do not stratify this result by viral load.

- The proportion of patients with different genotypes, in multi-national clinical trials, is unlikely to be reflective of the genotype distribution in the UK. Hence the overall sustained virological response is unlikely to provide a good indication of response. As a result, where possible, patient genotypes have been modelled separately adopting commonly used groupings of “difficult to treat” genotypes (genotype 1 and occasionally genotype 4) and more responsive genotypes (2 and 3).
- Baseline populations applied in the economic model were based on data, for new and existing patients, from a clinical audit in a liver unit at a London teaching hospital. Clinical advisors to this project confirmed that the distribution of patients across disease stages agreed with their clinical experience. However, it is not clear how closely these distributions, or the assumed mean age of patients at the start of the model, relate to the characteristics of patients in the sub-groups of patients covered by this review. The clinical audit data pre-dates NICE guidance on the use of peginterferons in patients with chronic HCV (TA75 and TA106) and it is not clear how the distribution of patients across disease stages may have changed – particularly given recent guidance on treating patients with mild disease (TA106). However there is generally very little information on the age and stage of disease for treated patients – the latter becoming less relevant to decisions to initiate treatment, but remain relevant to modelling response to treatment where cirrhotic patients appear less likely to achieve SVR.
- Disease progression parameters included in the model were derived from large cohort studies in relevant (European) populations. The parameters have been used in previous economic evaluations and ensure consistency between appraisals. Input parameters for fibrosis progression (from mild to moderate and from moderate to compensated cirrhosis)

were taken from a recent analysis using biopsy data from a UK cohort study. Where evidence suggests that differential progression rates should be applied for the sub-groups covered by this assessment (e.g. fibrosis progression in HCV/HIV co-infected patients) this has been addressed in additional analyses in this report.

- Quality of life/health state utility weights in the model were taken from reports on a multi-centre trial and observational study, conducted using the EQ-5D and valued using the UK general population tariff. The population of patients recruited to the UK trial were treatment-naïve patients with mild HCV and this was supplemented by an observational study recruiting patients with compensated and decompensated cirrhosis. It is not clear how applicable these quality of life weights are to some of the sub-groups of patients in the current assessment – re-treated patients are likely to be older while quality of life assessments for mono-infected patients may not be directly applicable to those with HCV/HIV co-infection.
- Health state costs included in the model, taken from the UK Mild Hepatitis C trial, were developed in an observational study alongside the trial. Intervention costs were based on treatment protocols developed as part of our previous assessment in collaboration with UK clinical experts and valued using reference costs from an NHS Hospital Trust. All costs were inflated to current costs using the HCHS Pay and Prices Index. It is not clear how adequately the treatment protocols may capture the complexity of managing patients with HCV/HIV co-infection - the sensitivity of the cost-effectiveness results to the costs of managing anti-viral treatment in this group of patients was addressed in a sensitivity analysis.

## **Issues for consideration**

The main issues relating to this appraisal are summarised below.

**Definitions and reporting:** Rapid virological response and low viral load were not consistently defined across the trials included in the assessment

report. The lower limits of detection of the virus were also different between trials. This variability in cut-off limits has implications for the number of people classified as having low viral load or achieving a rapid virological response. Sustained virological response was not reported according to the stage of liver disease in the included studies. Peginterferon alfa is indicated for people with compensated liver disease and is therefore likely to be given to people with compensated cirrhosis. The latter condition has been shown consistently in other chronic HCV studies to be associated with poorer outcome in terms of sustained virological response. The assessment report attempted to address this in the sensitivity analysis.

**Baseline populations:** The baseline populations applied in the economic model were derived from a clinical audit in a liver unit at a London teaching hospital. It is not clear how closely these distributions, or the assumed mean age of the people at the start of the model, relate to the characteristics of people in the subgroups covered in this appraisal. The data pre-dates NICE guidance on the use of peginterferons in people with chronic HCV so it is not clear how the distributions of people across disease stages may have changed with current treatment regimens.

**Early stopping rules:** The adoption of early stopping rules (in these analyses the cut off was set as no early virological response at 12 weeks) substantially reduced the ICERs for each group re-treated. The Royal College of Physicians states that early stopping rules could be made more stringent by specifying a negative or undetectable HCV RNA at 12 weeks (complete early virological response).

**Dosing:** Two of the RCTs of peginterferon alfa-2a included in the systematic review of clinical-effectiveness used doses of ribavirin according to body weight, which is no longer within the licenced indication. Both of these trials restricted inclusion to genotype 2 or genotype 2/3 patients. The product licence for peginterferon alfa-2a specifies that ribavirin should be given in a



fixed dose of 800mg in genotypes 2 and 3. Both trials appear to have been designed and executed before the licence variation. Exclusion of these RCTs solely on this basis would have further reduced the evidence base such that there would be no evidence of the impact of shortened treatment durations in patients with genotypes 2 or 3.

**Comparators:** The majority of studies used to derive estimates of response to treatment with peginterferon alfa did not make the comparisons specified in the decision problem. For re-treatment of patients who did not respond or relapsed following previous treatment and also patients with HCV/HIV co-infection the specified comparator was supportive care, while the clinical trials have active comparators. The Assessment Group was unable to construct evidence networks that included placebo (or supportive care) controlled trials. As a result, in common with the manufacturers, the Assessment Group conducted their comparison with supportive care by assuming that the spontaneous sustained virological response rates will be zero. While this is generally supported by clinical opinion, it remains an assumption and is not supported by robust evidence.

**Model Inputs:** Parameters in the models (disease progression, utility and health state cost) have not been derived for the specific patient sub-groups in this assessment. Targeted searches undertaken by the Assessment Group did not identify suitable data, for the relevant patient groups, for the majority of parameters in the model. It is not clear how applicable health state utility values for HCV mono-infected are to patients with HCV/HIV co-infection. Similarly, treatment costs based on protocols for mono-infected patients may underestimate the resource use required for on-treatment management of HCV/HIV co-infected patients. The Assessment Group attempted address this through sensitivity analyses.

Sustained virological response has not been reported according to stage of liver disease in the included studies. However peginterferon alfa treatment is

indicated for patients with compensated liver disease and is therefore likely to be provided to patients with compensated cirrhosis. Fibrosis stage (particularly cirrhosis) has been shown consistently (in other populations of patients with chronic HCV) to be associated with poorer outcome in terms of sustained virological response. The Assessment Group attempted to address this by including sensitivity analyses adopting a lower probability of sustained virological response in cirrhotic patients.

**Quality of life and health state utility weights:** In the Assessment Group's model, quality of life and health state utility weights were taken from reports on a multicentre trial that recruited treatment-naïve people with mild HCV. It is possible that the values derived from the trial may not be representative of utilities for people who have been previously treated or that the values may overestimate the health utility for HCV/HIV co-infected people.

## **Ongoing research**

The following study is currently recruiting participants:

NCT00532701. Peginterferon alfa-2a and ribavirin in patients with genotype 2 chronic hepatitis C: A randomised study of treatment duration and ribavirin dose stratified by rapid virological response.

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## Appendix A: Sources of evidence considered in the preparation of the overview

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 Submissions or statements were received from the following organisations:

Manufacturers/sponsors

Roche Products Ltd  
Schering-Plough Ltd

Professional/specialist, patient/carer and other groups:

Hepatitis C Trust  
Royal College of Physicians