# NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

## Overview

## Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C: Part-review of Technology Appraisal Guidance 75

The overview is written by members of the Institute's team of technical analysts. It forms part of the information received by the Appraisal Committee members prior to the first committee meeting. The overview summarises the evidence and views that have been submitted by consultees and evaluated by the Assessment Group, and highlights key issues and uncertainties. In order to allow sufficient time for the overview to be circulated to Appraisal Committee members prior to the first Appraisal Committee meeting, it is prepared before the Institute receives Consultees' comments on the Assessment Report. These comments are therefore not addressed in the Overview.

A list of the sources of evidence used in the preparation of this document is given in Appendix A.

# 1 Background

This review is being carried out specifically to determine the clinical effectiveness and cost effectiveness of extending the treatment currently provided to people with chronic hepatitis C (CHC) to include those with mild disease. The treatment recommended by NICE for people with moderate or severe disease is a combination of pegylated interferon alfa (2a or 2b) and ribavirin. At the time that the initial appraisal was carried out, two studies on the treatment of people with mild CHC were almost complete, but it was decided that the appraisal should not be delayed until the results of these studies were reported.

**Current guidance (TA 75)**

1.1 Combination therapy with pegylated interferon alfa (peginterferon alfa) and ribavirin is recommended within its licensed indications for the treatment of people aged 18 years and over with moderate to severe 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 the full guidance) 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*

Chronic hepatitis C is a disease of the liver caused by the hepatitis C virus (HCV). Generally the virus is transmitted parenterally but the natural history of the disease is not completely understood. It may be acquired through intravenous drug use and the sharing of needles. It was spread through blood products before the viral inactivation programme was implemented in the mid-1980s, and it was spread through blood transfusions before the introduction of screening in 1991. There is also a small risk associated with tattooing, electrolysis, ear piercing and acupuncture. Infection through sexual intercourse can also occur. There is a transmission rate of about 6% from mother to child if the mother is an HCV carrier. Concomitant HIV infection increases the risk of transmission.

Patients are often asymptomatic after exposure to the virus but about 20% will develop acute hepatitis; some of these people will experience non-specific symptoms including malaise, weakness and anorexia. Up to 85% of those exposed fail to clear the virus and go on to develop chronic hepatitis. The rate of progression of the disease is slow but variable, taking about 20–50 years. 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 patients with end-stage liver disease or hepatocellular carcinoma may require liver transplantation.

The ability of patients to rid themselves of the virus is related to the genotype of the virus, which affects the ability of the immune system to mount an effective response. Six major genetic types of HCV have been found. Genotype 1 is the most common in the UK, accounting for about 40–50% of cases. Genotypes 2 and 3 contribute another 40–50%, and genotypes 4, 5 and 6 constitute the remainder, about 5%.

Estimates of the numbers of people infected with HCV in England and Wales vary between 200,000 and 600,000, with recent estimates being towards the top of this range. (In 2005, the Department of Health estimated that only 47,000 of people with HCV infection had been diagnosed and only 7,000 had been treated.) There is also great variation in prevalence between certain subgroups of the population: 0.04% in blood donors, 0.4% in people attending antenatal clinics in London, 1% in people attending genito-urinary clinics and up to 50% in intravenous drug users.

Since it is not possible in the short term to directly measure the effectiveness of treatment in reducing progression to cirrhosis and hepatocellular carcinoma, three surrogate markers have been used in trials: hepatic histology, virological loss of HCV-RNA (by quantitative polymerase chain reaction), and levels of alanine aminotransferase (an enzyme that indicates liver inflammation, known as ALT).

## *1.2 Current management*

Current NICE guidance applies only to people with moderate to severe CHC, defined as histological evidence of significant scarring (fibrosis) and/or significant necrotic inflammation. For the vast majority of patients with moderate or severe hepatitis C, the standard treatment is combination therapy with peginterferon alfa-2a or

peginterferon alfa-2b together with ribavirin. Monotherapy with peginterferon alfa is used only for people unable to tolerate ribavirin.

For people with HCV genotypes 2 or 3, the proportion of patients with a sustained virological response (SVR)[1] to peginterferon alfa and ribavirin in trials was of the order of 75–85%. For genotype 1, the SVR rate was of the order of 40–50%, while for the three less frequent genotypes (4, 5 and 6) the SVR rate appears to be between the SVR rates for genotype 1 and genotypes 2 and 3.

For people with genotypes 2 or 3, the SVR is attained after 24 weeks of treatment. Further treatment does not increase the SVR rate, so treatment beyond 24 weeks is not advised. For the other genotypes, it may take longer than 24 weeks for people to gain an SVR, so the standard treatment length is 48 weeks. However, if no virological response has occurred by 12 weeks of treatment, an SVR is unlikely to occur. Hence, patients who do not show sufficient virological response at 12 weeks will not be given the further 36 weeks of treatment. A test of virological response at 12 weeks is not required for people infected with genotypes 2 or 3, because almost all respond at that time.

It is necessary to mention a little about the technology that peginterferon alfa therapy replaced. That therapy was a combination of non-pegylated interferon alfa and ribavirin. The pegylation process increases the half-life of the interferon molecule in the body from about 4 hours to about 40 hours (peginterferon alfa-2b) or 50–130 hours (peginterferon alfa-2a). Accordingly, patients need to inject the interferon only once per week with peginterferon alfa therapy compared with the three times per week needed with non-pegylated interferon. In addition, clinical trials suggest that response rates to interferon among patients with moderate and severe disease are significantly lower than with peginterferon therapy.

To determine whether a person with CHC has reached the moderate or severe stage of the disease, it has been the practice for the person to have a liver biopsy before interferon alfa or peginterferon alfa therapy is prescribed. For people with genotypes 2 or 3, the requirement for a biopsy before starting peginterferon alfa therapy has been dropped from the marketing authorisations.

# 2 The technology

The purpose of this appraisal is to determine whether to extend treatment to include not only the patients with moderate or severe CHC but also those with mild disease. For people with mild disease, the comparator should be a strategy of waiting and treating the disease only if it progresses to moderate or severe.

[1] Virological response is considered to be sustained when HCV RNA remains non-detectable for at least six months after discontinuation of treatment.

**Table 1 Summary description of technology**

| Generic name | Pegylated interferon alfa-2a and ribavirin | Pegylated interferon alfa-2b and ribavirin |
|---|---|---|
| Proprietary name | Pegasys and Copegus | ViraferonPeg and Rebetol |
| Manufacturer | Roche | Schering-Plough |
| Dose: genotypes 2 and 3 | Peginterferon alfa-2a (Pegasys) 180 micrograms once per week plus ribavirin (Copegus) 800 mg per day for 24 weeks | Peginterferon alfa-2b (ViraferonPeg) 180 micrograms once per plus ribavirin 800mg per day (< 65 kg body weight) or 1000 mg per day (65–85 kg) or 1200 mg per day (> 85 kg) for 24 weeks |
| Dose: genotypes 1, 4, 5 and 6 | Peginterferon alfa-2a 180 micrograms once per week for at least 24 weeks (low viral load) or for 48 weeks (high viral load) plus ribavirin 1000 mg per day (< 75 kg body weight) or 1200 mg day (> 75 kg) for same length of time as peginterferon alfa | Peginterferon alfa-2b 180 micrograms once per week for at least 24 weeks (low viral load) or for 48 weeks (high viral load) for plus ribavirin 800 mg per day (65 kg body weight) or 1000 mg per day (65–85 kg) or 1200 mg per day (> 85 kg) for same length of time as peginterferon alfa |
| Acquisition cost excluding VAT (BNF edition 50) | For genotypes 2 and 3: £5,019 for 24 weeks. For genotype 1 £10,963 or £11,889 for 48 weeks depending on weight<br>Monotherapy: for genotypes 2 and 3, £3,169 for genotype 1, £6,339 | For genotypes 2 and 3: from £3,862 for < 40 kg body weight to £8,280 for > 85 kg; £6,734 for average weight of 79 kg. For genotype 1: from £7,725 (< 40 kg) to £16,559 (> 85 kg); £13,468 for average weight.<br>Monotherapy: for genotypes 2 and 3, from £1,657 to £4,972 and for genotype 1 from £3,314 to £9,943 |

Standard haematological tests and blood chemistry (that is, full blood count and differential platelet count, liver function tests, uric acid, serum bilirubin and serum creatinine) are necessary for all patients being considered for combination therapy. Where required, liver biopsy should be undertaken in patients for whom there are no increased risks in order to assess liver scarring and necro-inflammation, using an accepted severity scale. Patients should be seen weekly for the first 4 weeks of treatment and then monthly for 6 months to check for haemolysis and changes in thyroid activity. The HCV genotype with which the patient is infected should also be determined for all candidates for combination therapy.

Both pegylated and non-pegylated interferon give rise to flu-like symptoms in many patients, while ribavirin leads in a proportion of cases to anaemia, pruritus, rash, insomnia and dyspnoea.

# 3 The evidence

## *3.1 Clinical effectiveness*

The standard measurement of effectiveness for treatment of CHC is the virological response rate sustained for 6 months (SVR rate). This is defined as the proportion of patients in whom the virus is undetectable in blood samples 6 months after treatment has been completed.

A direct measure of viral activity is viral load, which is the number of copies of the virus in a given quantity of blood. Although a high viral load is likely to mean that the liver deteriorates more quickly than it does under the influence of a low viral load, the relationship is not a simple one, and some people live with high viral loads for many years without progressing from mild to moderate CHC.

Whether a person has mild or moderate CHC is determined by the extent of liver damage. Wherever possible, this is determined histologically from a biopsy. The main indicator of liver damage is the degree of fibrosis present, although the degree of necro-inflammation also contributes to the diagnosis. There are a number of scoring systems used for this purpose, the most common being the Knodell, Ishak and METAVIR. These classification systems differ slightly in their definitions of mild CHC (see section 2.1.2.2 of the Assessment Report, pages 24–26).

Five trials of interferon alfa-2b and 3 trials of peginterferon alfa-2a that included patients with mild CHC were included in the assessment report. All studies included the combination with ribavirin in at least one arm. The definition of mild CHC for the purposes of this appraisal is based on guidelines issued by the Royal College of Physicians and the British Society of Gastroenterology,[2] but the assessment group noted that threshold between mild and moderate CHC in terms of fibrosis score can be arbitrary. In determining the inclusion criteria for this review, the Assessment Group chose to class trials as having been conducted in mild CHC if at least 70% of the patients enrolled had CHC that was classed as mild. They also considered for inclusion trials that presented data for the subgroup of patients with mild CHC separately (see section 4.1.4 of the Assessment Report where results from a further 11 trials are reported).

The comparators in the trials varied. Two of the three peginterferon alfa studies compared longer courses (48 weeks) with shorter courses (24 weeks) while the third compared peginterferon alfa-2a with non-pegylated interferon alfa-2a.

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[2] Clinical guidelines on the management of hepatitis C, Royal College of Physicians of London and the British Society of Gastroenterology, J C L Booth, J O'Grady, J Neuberger, 2001

None of the studies in the assessment report have compared the strategies of early treatment of mild disease with a strategy of watchful waiting and treatment of those who progress to moderate or severe disease. Since this is the primary comparison of interest in this appraisal, results for the comparator arms in the above studies are not reported below. These can be found in the relevant tables in the assessment report.

Since viral genotype seems to be the most important factor determining the effectiveness of treatment, this overview reports the results of the studies by subgroup according to genotype (one study only reported results in this way). Overall SVR rates for the total populations (where reported) can be found in tables 7 and 8 of the assessment report.

### 3.1.1 Peginterferon alfa-2a (Pegasys) plus ribavirin

#### *HCV genotypes 2 and 3*

The three trials of peginterferon alfa 2a + ribavirin yielded 72–84% SVR rates for 24 weeks of treatment and 78–80% for 48 weeks of treatment. For people infected with these genotypes, there was no significant difference between the SVR rates after 24 weeks or 48 weeks of treatment. These results are consistent with those for studies conducted in people with moderate-to-severe CHC; in the previous appraisal, the corresponding SVR rates in different trials including people with both mild and moderate-to-severe CHC was 79%.

#### *HCV genotype 1*

Peginterferon alfa-2a + ribavirin yielded 13–42% rates of SVR for 24 weeks of treatment and 40–52% for 48 weeks of treatment. For people infected with genotype 1, the additional 24 weeks of treatment significantly increased the SVR rate, as it did for people with moderate-to-severe CHC. For comparison, in the previous appraisal the corresponding SVR rates in different trials including people with both mild and moderate-to-severe CHC was estimated at 46% after 48 weeks of treatment.

#### *HCV genotypes 4, 5 and 6*

The proportion of people with these genotypes in trials (as in populations of those with CHC throughout much of the world) was small, but the effect of treatment for these genotypes appears to fall between those for genotype 1 and genotypes 2 and 3, although it is closer to genotype 1. This appears to hold for all other treatments discussed below, and it will not be separately mentioned again.

### 3.1.2 Peginterferon alfa-2b (ViraferonPeg) plus ribavirin

Although there was no trial of peginterferon alfa-2b combination therapy that met the Assessment group's criteria for inclusion as trials in patients with mild CHC, the Manns trial (2001) included 1,014 (of 1,530) participants who had been documented as having no or minimal fibrosis.

For those on high-dose (1.5 micrograms/kg per week for 48 weeks) peginterferon alfa 2b + ribavirin, SVR rates of 57% (out of 333 participants) were recorded among those with no or minimal fibrosis (that is, mild CHC) compared with

44% (out of 136 participants) among those with bridging fibrosis or cirrhosis (that is, moderate-to-severe CHC). For those on low-dose (1.5 micrograms/kg per week for four weeks, then 0.5 micrograms/kg per week for 48 weeks) peginterferon alfa-2b + ribavirin, SVR rates of 51% were recorded among those with mild CHC (345 participants) compared with 43% among those with moderate-to-severe CHC(146 participants). Results by genotype have not been reported. The rates of SVR among participants on high-dose peginterferon alfa-2b combination therapy was significantly higher than that of patients on non-pegylated interferon 2b + ribavirin while the SVR was not higher for those on the lower dose of peginterferon alfa-2b.

### 3.1.3 Interferon alfa-2a (Roferon A) plus ribavirin

No trials of non-pegylated interferon alfa-2a + ribavirin in mild CHC were included in the assessment report as trials in mild CHC. One study evaluating induction therapy with interferon alfa-2a plus ribavirin followed by interferon alfa-2a monotherapy reported subgroup results and is summarised in section 4.1.4.2 of the assessment report.

### 3.1.4 Interferon alfa-2b (Viraferon/Intron A) plus ribavirin

Five trials of interferon alfa-2b + ribavirin that met the Assessment Group's inclusion for trials in patients with mild CHC were identified (aggregate size: 656 people).

#### *HCV genotypes 2 and 3 (in some trials genotype non-1)*

The studies of interferon alfa-2b + ribavirin yielded SVR rates of 49–81%. (From the previous appraisals, the corresponding SVR in different trials for people with a mixture of mild and moderate-to-severe CHC averaged about 70%.) For people infected with these genotypes, there was no significant difference between the SVR rates after 24 weeks or 48 weeks of treatment (this was also true in the previous appraisal that considered people with moderate-to-severe CHC).

#### *HCV genotype 1*

Interferon alfa-2b + ribavirin yielded 22–50% SVR rates following 24 weeks of treatment in two small trials and 18–38% following 48 weeks of treatment in three small trials. (From previously reviewed trials, the corresponding SVR in different trials for people with a mixture of mild and moderate-to-severe CHC was 17% at 24 weeks and averaged 30% at 48 weeks.)

### 3.1.5 Monotherapy trials

People who are unable to take ribavirin and are treated with monotherapy with peginterferon alfa or non pegylated interferon alfa have much lower response rates than people treated with combination therapy. One trial of 159 people compared response rates for three dosage regimens of peginterferon alfa-2a and one for interferon alfa-2a. SVR rates were 3% for interferon alfa-2a and between 10% and 29% for peginterferon alfa-2a, depending on dose. Altogether, 82% of participants were classified as having mild CHC.

Another trial of 1,219 people compared response rates for three dosage regimens of peginterferon alfa-2b and one of interferon alfa-2b. Altogether, 83% of participants in

this study were classified as having mild CHC. SVR rates were 12% for interferon alfa-2b and between 18% and 23% for peginterferon alfa-2b, depending on dose. Altogether, 83% of participants in this study were classified as having mild CHC.

### 3.1.6 Factors influencing response

Viral genotype has by far the most influence on the efficacy of combination therapy. However, the following factors also appear to influence efficacy.

- Viral load: the higher the viral load, the lower the proportion of people with HCV who will have an SVR. This effect appears to be greater for people infected with genotype 1.
- Fibrosis: it appears that a greater extent of fibrosis of the liver indicates a lower probability of achieving a SVR.
- Age: treatment appears to work better for people younger than 40, but the effect is not marked.
- Race, and sex: these may have a small effect (white people and women appear to respond marginally better than black people and men).

***Summary***

Taken as a whole, the evidence for both combination therapy and monotherapy, and for both pegylated and non-pegylated interferon alfa 2a and 2b, suggests that SVR rates for patients with mild disease are about the same as those for patients with moderate or severe disease. Combination therapy with peginterferon alfa (2a or 2b) and ribavirin has higher SVR rates than combination therapy with non-pegylated interferon alfa (2a or 2b). The same is true of monotherapy.

## *3.2 Cost effectiveness*

For people with mild CHC, clinical trials suggest that peginterferon alfa-based combination therapy is more effective than interferon alfa-based combination therapy. For people with mild CHC, peginterferon alfa-based combination therapy, by extension of the results obtained previously for people with moderate and severe disease, is likely to be cost effective relative to non-pegylated interferon-based combination therapy. The more pertinent question is whether it is cost effective to treat people who have mild CHC immediately or to wait until they reach the moderate stage. If the rate of progression to moderate CHC were sufficiently low, it would be better not to subject all people with mild CHC to the significant side effects of treatment with combination therapy because few would progress to moderate disease or beyond.

### 3.2.1 Studies from the literature

The Assessment Report found six studies examining the cost effectiveness of treatment for patients with mild CHC. Three of these studies compared interferon combination therapy with no treatment rather than delayed treatment. These three studies showed that interferon combination therapy was cost effective when compared against standard care (all estimated mean incremental cost effectiveness ratios [ICERs] were under £10,000 per QALY). Two studies compared early treatment with peginterferon alfa combination therapy against delayed treatment.

They showed that for genotypes 2 and 3, early treatment is apparently cost effective when compared with delayed treatment, but the case for early treatment for genotype 1 is less clear.

### 3.2.2 Manufacturer submissions

The Roche model determined the cost effectiveness of peginterferon alfa-2a + ribavirin against no treatment. The estimated mean cost per QALY for treating patients with mild CHC was £1,000 for genotypes 2 and 3 and £4,000 for genotype 1.

The Schering-Plough model determined the cost effectiveness of peginterferon alfa-2b + ribavirin against no treatment. The model is academic-in-confidence. The estimated mean cost per QALY for treating mild CHC was £….. for genotypes 2 and 3 and £….. for genotype 1.***[Academic in confidence material removed]***

### 3.2.3 Assessment Report

The model developed by the Assessment Group considers eight health states: remission, mild CHC, moderate CHC, compensated cirrhosis, decompensated cirrhosis, liver cancer, liver transplantation and death. It takes SVR rates from the manufacturers' submissions and the transition rates between health states from a number of sources. For example, the estimated transition rate from mild to moderate CHC as used in the model is 2.5% per year. Health-state utilities and costs were estimated from the UK mild hepatitis C trial. For comparability with the previous review, benefits were discounted at 1.5% and costs at 6% per year, with a sensitivity analysis at 3.5% for both costs and benefits.

It is important to remember that the most relevant comparisons are those of early treatment of mild CHC against deferring treatment until moderate CHC is reached.

#### *HCV non-1 genotypes*

The base case estimated mean ICER for watchful waiting followed by treatment with peginterferon alfa-2a combination therapy when the disease reaches the moderate to severe stage relative to best supportive care (no treatment) is £1,300 per QALY. The corresponding ICER for peginterferon alfa-2b plus ribavirin is £1,400. For non-pegylated interferons, the corresponding ICERs are between £1,500 and £3,000 per QALY.

The mean ICERs for early treatment with peginterferon alfa in combination with ribavirin against deferring treatment until the disease reaches the moderate to severe stage in people with HCV genotype non-1 infection are £3,700 for peginterferon alfa-2a and £4,300 for peginterferon alfa-2b. For non-pegylated interferons, the corresponding ICERs are between £3,500 and £5,000 per QALY.

In a deferred treatment strategy (that is, watchful waiting followed by treatment of moderate-to severe disease) in non-genotype 1 HCV, peginterferon alfa-2a either dominates non-pegylated interferon or has a low ICER at £250 per QALY depending on the estimate of SVR rate used in the model. In an early treatment strategy,

peginterferon alfa-2a has an ICER of £2,700 per QALY compared with non-pegylated interferon. For peginterferon alfa-2b the corresponding ICERs are £1,000 per QALY (deferred treatment strategy) and £4,000 per QALY (early treatment strategy).

In people unable to take ribavirin, monotherapy with pegylated or non-pegylated interferon may be used. The mean ICER for early treatment with peginterferon alfa monotherapy against the same treatment deferred to a later stage is £3,000 per QALY for peginterferon alfa-2a and £2,300 for peginterferon alfa-2b.

***HCV genotype 1***

The base case estimated mean ICER for peginterferon alfa-2a combination therapy deferred until the disease reaches the moderate to severe stage relative to best supportive care (no treatment) is £6,900 per QALY. The corresponding ICER for peginterferon alfa-2b plus ribavirin is £4,700. For non-pegylated interferons, the corresponding ICERs are between £7,800 and £19,000 per QALY.

The mean ICERs for early treatment with peginterferon alfa in combination with ribavirin against deferring treatment until the disease reaches the moderate to severe stage in people with HCV genotype 1 infection are £10,300 for peginterferon alfa-2a and £8,300 for peginterferon alfa-2b. For non-pegylated interferons, the corresponding ICER is between £9,000 and £16,000 per QALY.

Early treatment with peginterferon alfa-2a compared to early treatment with non-pegylated interferon in HCV genotype 1 infection has an ICER of £10,000 per QALY. Due to the higher SVR reported for peginterferon alfa-2b the QALY gain is greater: the ICER for early treatment with peginterferon alfa-2b relative to non-pegylated interferon is £4,800 per QALY. The corresponding ICERs for comparisons of peginterferon alfa with non-pegylated interferon in deferred treatment strategies are £4,700 per QALY for peginterferon alfa-2a and £1,500 per QALY for peginterferon alfa-2b.

***Sensitivity analyses***

Estimated mean ICERs are even lower using current stopping rules.

Sensitivity analysis does not lead to ICERs over £20,000 except when the average age of patients is increased by 15 years.

# 4 Issues for consideration

The main issues are summarised below.

- The role of patient choice: some patients may decide not to have treatment while the disease remains in its mild state (because of anticipated adverse events and/or intolerance to treatment).

- The role of biopsy: because treatment of mild CHC is clinically effective and would seem to be cost effective against deferring treatment until the moderate state is reached, biopsy to determine disease stage for the purpose of deciding whether to treat does not appear to be required. (Whether biopsy is indicated for other reasons is not within the scope of this appraisal.) A biopsy may be indicated to confirm mild disease if a patient wishes to defer treatment. This needs to be taken into account when making this decision.

- The infectivity of the disease: This aspect has not been accounted for in any of the models. A person who is cured of HCV infection cannot pass the disease on. Given that currently about 3,000 people are being treated out of the 200,000–600,000 who are infected, it is not clear how much effect the curing of, say, 1,500 people per year would have on future infection rates. Although we cannot determine magnitudes of effect, we certainly know that omitting this aspect of the effect of treatment will underestimate the benefits of treatment.

- From the Schering-Plough submission: 'the Phase IV trial P01882 suggests that genotype 2/3 patients who have undetectable HCV RNA after four weeks need only 12 weeks of therapy, while those of genotype 1 with low viral load (< 2 million copies/ml) need only 24 weeks of therapy.'

The Committee may wish to refine the stopping rules to reflect this new data, but it may believe that it is beyond the scope of this review.

The submission continues: 'Applying these more stringent stopping rules would reduce the average cost per course of therapy by 17% to £6,523 per patient. These more stringent stopping rules have not yet been incorporated into the licensed indications.'

# 5 Authors

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# 6 Appendix A. Sources of evidence considered in the preparation of the overview

A Jonathan Shepherd, Jeremy Jones, Debbie Hartwell, Peter Davidson, Alison Price, Norman Waugh. Southampton Health Technology Assessments Centre *Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C – a systematic review and economic evaluation.* October 2005

B Submissions from the following organisations:

I Manufacturer/sponsors:

- Roche Products Ltd.
- Schering-Plough Ltd.

II Professional/specialist and patient/carer groups:

- Hepatitis C Trust
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians