National Institute for Health and Clinical Excellence

UPDATE

This guidance has been partially updated by 'Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C' (NICE technology appraisal guidance 200 [TA200]). The recommendations that have been updated are indicated in section 1 below. See TA200 (www.nice.org.uk/guidance/TA200) for details of the new recommendations and evidence considered.

Issue date: August 2006

Review date: November 2007

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

This is an extension of the guidance given in NICE technology appraisal guidance 75

NICE technology appraisal guidance 106

NICE technology appraisal guidance 106
Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C

Ordering information

You can download the following documents from www.nice.org.uk/TA106

- The full guidance (this document).
- A quick reference guide for healthcare professionals.
- Information for people with mild chronic hepatitis C and their carers ('Understanding NICE guidance').
- Details of all the evidence that was looked at and other background information.

For printed copies of the quick reference guide or 'Understanding NICE guidance', phone the NHS Response Line on 0870 1555 455 and quote:

- N1099 (quick reference guide)
- N1100 ('Understanding NICE guidance').

This guidance is written in the following context

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

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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.

September 2010: This guidance has been partially updated by 'Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C' (NICE technology appraisal guidance 200) as shown below.

1 Guidance

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).~~

These recommendations have been updated and replaced by NICE technology appraisal guidance 200.

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.

2 Clinical need and practice

2.1 Chronic hepatitis C is a disease of the liver caused by the hepatitis C virus. Generally the virus is transmitted parenterally, but the natural history of the disease is not completely understood. The virus is primarily acquired through percutaneous exposure to contaminated blood. 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. However, injecting drug use, cosmetic and other practices involving percutaneous exposure remain common routes of transmission. HCV prevalence is correlated with markers of sexual activity, but HCV incidence in monogamous heterosexual partners of infected people is extremely low. 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.

2.2 People infected with HCV are often asymptomatic, but about 20% will develop overt hepatitis. Many people who are chronically infected will experience non-specific symptoms including malaise, weakness and anorexia. About 80% of those exposed go on to develop chronic hepatitis. The rate of progression of the disease is slow but variable, usually taking about 20–50 years from the time of infection. About 30% of those who are infected develop cirrhosis within

20–30 years, and a small percentage of these people are at a high risk of developing 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 need liver transplantation.

2.3 The effectiveness of treatment is related to the genotype of the virus. 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%.

2.4 Recent estimates suggest that approximately 200,000 to 500,000 people are infected with HCV in England and Wales. (In 2005, the Department of Health estimated that only 47,000 people with HCV infection had been diagnosed and only 7000 had been treated.) There is also great variation in prevalence between subgroups of the population: 0.04% in blood donors, 0.4% in people attending antenatal clinics in inner London, 1% in people attending genitourinary clinics and up to 50% in intravenous drug users attending drug abuse clinics.

2.5 Because 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)
- levels of alanine aminotransferase (an enzyme that indicates the presence of liver inflammation).

2.6 The previous NICE guidance (TA 75) applies only to people with moderate or severe chronic hepatitis C, which is defined as histological evidence of significant scarring (fibrosis) and/or significant necrotic inflammation of the liver. For the majority of people with moderate or severe hepatitis C, the

standard treatment is combination therapy with ribavirin and either peginterferon alfa-2a or peginterferon alfa-2b. Monotherapy with peginterferon alfa is used only for people unable to tolerate ribavirin.

2.7 In trials for people with moderate or severe hepatitis C, about 75–85% of people with HCV genotype 2 or 3 had a sustained virological response 6 months after finishing a course of treatment with peginterferon alfa and ribavirin. For people with genotype 1, the rate of sustained virological response was about 40–50%, while for the three less common genotypes (4, 5 and 6) the rate appears to be between those for genotype 1 and genotypes 2 or 3.

2.8 For people with moderate or severe disease and with genotype 2 or 3, the maximum rate of sustained virological response is attained after 24 weeks of treatment. Further treatment does not increase the rate, so treatment beyond 24 weeks is not advised. For people with the other genotypes, it may take longer than 24 weeks to gain a sustained virological response, so the standard treatment length is 48 weeks. However, if no virological response has occurred by 12 weeks of treatment, a sustained response is unlikely to occur. Hence, it is recommended that people who do not attain a sufficient virological response by 12 weeks should not receive a further 36 weeks of treatment. People infected with genotypes 2 or 3 do not need a test of virological response at 12 weeks, because almost all respond by that time.

2.9 Peginterferons are formed by attaching strands of polyethylene glycol (PEG) to the interferon molecules. This slows the rate of absorption and excretion of interferon, reducing the fluctuations in serum concentrations that occur with unmodified interferon. The pegylation process increases the half-life of the interferon molecule in the body: in the case of peginterferon alfa-2a from about 4 hours to between 50 and 130 hours, and for peginterferon alfa-2b from about 4 hours to about 40 hours. Accordingly, people treated with peginterferon alfa need injections only once a week, compared with three times a week for people treated with non-pegylated interferon, referred to in

this guidance as ‘interferon’. In addition, clinical trials suggest that response rates to interferon among people with moderate or severe disease are significantly lower than response rates to peginterferon therapy.

2.10 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. The HCV genotype with which the person is infected should be determined for all candidates for combination therapy. Liver biopsy has played a role in helping to determine disease staging, but it is no longer considered necessary for people with HCV of genotypes 2 and 3, or if biopsy poses an increased risk. 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.

2.11 Both pegylated interferon and interferon give rise to flu-like symptoms in many people. Ribavirin leads, in a proportion of cases, to anaemia, pruritus, rash, insomnia and dyspnoea. For full details of side effects and contraindications, see the summary of product characteristics for each drug.

2.12 The standard measurement of the effectiveness of treatment, in people with chronic hepatitis C, is the virological response rate sustained for 6 months (known as the sustained virological response rate). This is defined as the proportion of people in whom the virus is undetectable in blood samples 6 months after treatment has been completed.

2.13 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 disease to moderate disease.

2.14 A person is classified as having mild, moderate or severe chronic hepatitis C based on the extent of liver damage. If there is a sufficient need to know the extent of liver disease, this may be determined histologically by liver biopsy. The main indicator of liver damage is the degree of fibrosis, although the degree of necroinflammation also contributes to the diagnosis.

2.15 At a time before the treatment of mild chronic hepatitis C was routinely considered, it was the practice to perform a liver biopsy before prescribing interferon alfa or peginterferon alfa to determine whether a person with chronic hepatitis C had reached a moderate or severe stage of the disease. Initiating treatment at an earlier stage means this is no longer necessary.

3 The technology

3.1 The objective of this appraisal is to compare the use of peginterferon therapy (in combination with ribavirin or as monotherapy) in mild chronic hepatitis C with the current practice of deferring treatment until the disease has progressed to moderate or severe. Current practice and the technology are described in section 2 above.

3.2 Peginterferon alfa-2a (Pegasys) and ribavirin (Copegus) are manufactured by Roche. For genotypes 2 and 3, the licensed regimen is peginterferon alfa-2a 180 micrograms once per week plus ribavirin 800 mg/day for 24 weeks. This course of therapy costs £5019 (excluding VAT; 'British national formulary', 50th edition). For genotypes 1, 4, 5 and 6, the regimen is peginterferon alfa-2a 180 micrograms once per week for 48 weeks plus ribavirin 1000 mg/day (for people weighing less than 75 kg) or 1200 mg/day (for those weighing 75 kg or more) for the same length of time as peginterferon alfa. The cost is £10,963 or £11,889 for 48 weeks depending on body weight. For peginterferon monotherapy, the cost of treatment is £6339 (for 12 months) for all genotypes.

3.3 Peginterferon alfa-2b (ViraferonPeg) and ribavirin (Rebetol) are produced by Schering-Plough. For genotypes 2 and 3, the licensed regimen is

peginterferon alfa-2b 1.5 micrograms/kg/week plus ribavirin 800 mg/day (for people weighing less than 65 kg) or 1000 mg/day (for those weighing 65–85 kg) or 1200 mg/day (for those weighing more than 85 kg) for 24 weeks. The cost of a course is £6734 for a person of an average weight of 79 kg (excluding VAT; 'British national formulary', 50th edition). Costs may vary in different settings because of negotiated procurement discounts.

3.4 The marketing authorisation for peginterferon alfa 2b in combination with ribavirin has been varied and now allows for 24 weeks of treatment in people with genotype 1 (low viral load) who have responded sufficiently to treatment at 4 weeks. The cost is £6734 for a person of average weight (79 kg). For people with genotype 1 (high viral load) and optionally for those with low viral load, the cost for 48 weeks of treatment is £13,468 for a person of average weight (excluding VAT; 'British national formulary', 50th edition). Costs may vary in different settings because of negotiated procurement discounts.

3.5 For genotypes 5 and 6, the regimen (and associated cost) is as for genotypes 1 and 4 (high viral load). Costs may vary in different settings because of negotiated procurement discounts.

3.6 The cost of treatment for 24 weeks with peginterferon alfa-2b monotherapy is £1657 (0.5 micrograms/kg/week) or £2652 (1.0 micrograms/kg/week) and for 48 weeks is £3314 (0.5 micrograms/kg/week) or £5303 (1.0 micrograms/kg/week) (excluding VAT; 'British national formulary', 50th edition). Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

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

4.1 Clinical effectiveness

4.1.1 Three trials of peginterferon alfa-2a and five trials of interferon alfa-2b that included people with chronic hepatitis C, at least 70% of whom had mild disease, were included in the assessment report. All studies included the combination with ribavirin in at least one arm. The comparators in the trials varied. Two of the three peginterferon alfa-2a studies compared longer courses (48 weeks) with shorter courses (24 weeks); the third compared peginterferon alfa-2a with non-pegylated interferon alfa-2a.

4.1.2 No studies compared the strategies of early treatment of mild disease with a strategy of watchful waiting and treatment for those who progress to moderate or severe disease. Because this is the primary comparison of interest in this appraisal, results for the comparator arms in the studies in section 4.1.4 are not reported here.

Peginterferon alfa-2a plus ribavirin

4.1.3 HCV genotypes 2 and 3

4.1.3.1 The three trials of peginterferon alfa-2a plus ribavirin in people with genotypes 2 and 3 yielded sustained virological response rates of 72–84% after 24 weeks of treatment and rates of 78–80% after 48 weeks of treatment. For people infected with these genotypes, there was no statistically significant difference between the rates after 24 weeks of treatment or after 48 weeks. These results are consistent with those for studies conducted in people with moderate or severe chronic hepatitis C; in the previous appraisal (TA 75), the corresponding rate of sustained virological response in different trials that included people with both mild and moderate or severe disease was 79%.

4.1.4 HCV genotype 1

4.1.4.1 In people infected with genotype 1, peginterferon alfa-2a plus ribavirin yielded sustained virological response rates of 13–42% after 24 weeks of

treatment and 40–52% after 48 weeks. In this group, the additional 24 weeks of treatment statistically significantly increased the rate of sustained response.

Peginterferon alfa-2b plus ribavirin

4.1.5 Although there was no trial of peginterferon alfa-2b combination therapy that met the Assessment Group's criteria for inclusion of trials of people with mild chronic hepatitis C, one study included 1014 (of 1530) participants who had been documented as having no or minimal fibrosis. In this study, a sustained virological response occurred in 57% of participants with no or minimal fibrosis (that is, with mild disease) who received 'high-dose' peginterferon alfa-2b (1.5 micrograms/kg/week for 48 weeks) plus ribavirin. This compares with a rate of 44% among those who had bridging fibrosis or cirrhosis (that is, moderate or severe disease) who received high-dose peginterferon alfa-2b. In people who received 'low-dose' peginterferon alfa-2b (1.5 micrograms/kg/week for 4 weeks, then 0.5 micrograms/kg/week for 48 weeks) plus ribavirin, a sustained virological response rate of 51% was recorded among those with mild disease compared with 43% among those with moderate or severe disease. Results by genotype were not reported. The rate of sustained virological response was statistically significantly higher among participants on high-dose (but not low-dose) peginterferon alfa-2b combination therapy than among patients on non-pegylated interferon alfa-2b plus ribavirin.

Monotherapy trials

4.1.6 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 with three different regimens of peginterferon alfa-2a with one of interferon alfa-2a. Rates of sustained virological response were 3% for interferon alfa-2a and between 10% and

29% for peginterferon alfa-2a, depending on the dose. Altogether, 82% of participants were classified as having mild chronic hepatitis C.

4.1.7 Another trial of 1219 people compared response rates for three different regimens of peginterferon alfa-2b and one of interferon alfa-2b. Altogether, 83% of participants in this study were classified as having mild disease. Rates of sustained virological response were 12% for those treated with interferon alfa-2b and between 18 and 23% for those treated with peginterferon alfa-2b, depending on the dose.

Summary

4.1.8 Taken as a whole, the evidence for combination therapy and monotherapy, and for pegylated and non-pegylated interferon alfa-2a and pegylated and non-pegylated interferon alfa-2b, suggests that rates of sustained virological response among patients with mild disease are about the same as those among patients with moderate or severe disease. Combination therapy with peginterferon alfa (2a or 2b) and ribavirin produces higher rates of sustained virological response than combination therapy with non-pegylated interferon alfa (2a or 2b). Monotherapy with pegylated interferon alfa-2a or alfa-2b produces higher response rates than monotherapy with non-pegylated interferon alfa.

4.2 Cost effectiveness

4.2.1 The assessment report found six studies examining the cost effectiveness of treatment for people with mild disease. Three of these studies compared interferon combination therapy with no treatment rather than with delayed treatment. These three studies showed that interferon combination therapy was cost effective when compared with standard care (all estimated mean incremental cost-effectiveness ratios [ICERs] were less than £10,000 per quality-adjusted life year [QALY]). Two studies compared early treatment with peginterferon alfa combination therapy with 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.

4.2.2 The model employed in the Roche submission determined the cost effectiveness of peginterferon alfa-2a plus ribavirin against no treatment. The estimated mean cost per QALY for treating people with mild disease was £1000 for genotypes 2 and 3, and £4000 for genotype 1.

4.2.3 The model employed in the Schering-Plough submission determined the cost effectiveness of peginterferon alfa-2b plus ribavirin against no treatment. The model is academic-in-confidence. The estimated mean cost per QALY for treating mild chronic hepatitis C was £1000 for genotypes 2 and 3, and £3000 for genotype 1.

4.2.4 The model developed by the Assessment Group incorporated seven health states: remission, mild disease, moderate disease, compensated cirrhosis, decompensated cirrhosis, liver cancer and liver transplantation. It used rates of sustained virological response from the manufacturers' submissions and transition rates between the seven health states from a number of sources. For example, the estimated transition rate from mild to moderate disease as used in the model was 2.5% per year, which was obtained from observational data relating to 373 cases from a routine practice in a hospital in London between 1990 and 2001. 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% per year and costs at 6%, with a sensitivity analysis at 3.5% for both costs and benefits.

4.2.5 Non-1 genotype HCV

4.2.5.1 For people with non-1 genotype infection, the base case estimated mean ICER for deferring treatment with peginterferon alfa-2a combination therapy until the disease reaches the moderate or severe stage relative to best supportive care (no treatment) is £1300 per QALY. The corresponding ICER for peginterferon alfa-2b plus ribavirin is £1400. This

analysis confirms that the strategy of treating people with moderate or severe disease is cost effective compared with not treating them at all.

4.2.5.2 The estimated mean ICERs for early treatment with peginterferon alfa in combination with ribavirin are £3700 for peginterferon alfa-2a and £4300 for peginterferon alfa-2b, when compared with deferring treatment until the disease reaches the moderate-to-severe stage in people with non-1 genotype infection. This analysis shows that treatment of mild disease is cost effective compared with waiting until the patient reaches the moderate stage of the disease. These are the key cost-effectiveness estimates for this appraisal.

4.2.5.3 Further analysis shows that combination therapy with pegylated interferon is cost effective when compared with the corresponding non-pegylated therapy for treating people with mild disease.

4.2.6 Genotype 1 HCV

4.2.6.1 For people with genotype 1 infection, the base case estimated mean ICER is £6900 per QALY for watchful waiting followed by treatment with peginterferon alfa-2a combination therapy when the disease reaches the moderate or severe stage, relative to best supportive care (no treatment). The corresponding ICER for peginterferon alfa-2b plus ribavirin is £4700. This analysis confirms that the strategy of treating only moderate or severe disease is cost effective compared with not treating the infection at all.

4.2.6.2 For people with genotype 1 infection, the estimated mean ICERs for early treatment with peginterferon alfa in combination with ribavirin are £10,300 for peginterferon alfa-2a and £8300 for peginterferon alfa-2b when compared with deferring treatment until the disease reaches the moderate-to-severe stage, and reflecting the early stopping rules recommended in the summary of product characteristics for peginterferon alfa-2a. This analysis shows that treating mild disease is very likely to be cost effective

compared with waiting until the patient reaches the moderate stage. These are the key cost-effectiveness estimates for this appraisal.

4.2.6.3 Further analysis shows that pegylated interferon combination therapy is cost effective when compared with the corresponding non-pegylated therapy for treating people with mild disease.

4.2.7 Monotherapy: all genotypes

4.2.7.1 In people unable to take ribavirin, monotherapy with peginterferon may be used. The estimated mean ICER for early treatment with peginterferon alfa monotherapy is £3000 per QALY for peginterferon alfa-2a and £2300 for peginterferon alfa-2b against the same treatment deferred until a later stage.

4.2.8 Sensitivity analyses

4.2.8.1 Estimated mean ICERs are even lower using current stopping rules, whereby treatment is stopped at 12 weeks if a 100-fold reduction in viral load has not occurred.

4.2.8.2 Sensitivity analyses conducted in the assessment report do not lead to ICERs of more than £20,000 except when the average age of patients is increased by 15 years.

4.3 Consideration of the evidence

4.3.1 The Committee reviewed the data on the clinical effectiveness and cost effectiveness of interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C, having considered evidence on the nature of the condition and the value placed on the benefits of this treatment by people with the condition (or who have had the condition), those who represent them, and clinical experts. It was also mindful of the need to take account of the effective use of NHS resources.

4.3.2 The Committee heard from clinical and patient experts that studies show the quality of life of people with mild disease, even in the absence of histological evidence of definitive liver disease, is on average lower than that of people who have had mild disease and who have been cleared of the virus. The experts advised the Committee that such a difference in quality of life is an important contributor to the benefit of early treatment of mild disease.

4.3.3 The Committee also heard from the experts that sustained virological response, when the virus is undetectable 6 months after treatment has finished, is maintained for 10 years in more than 90% of people. Additionally, it is unusual for re-infection with HCV to occur after a sustained virological response has been achieved. These observations were consistent with the assumptions of the cost-effectiveness model used in the assessment report. Therefore, the Committee concluded that the model inputs were appropriate in these respects.

4.3.4 The Committee understood that about half of the approximately 3000 people in England and Wales who are treated each year have a sustained virological response and are effectively cured, but that the number of new cases is greater than the number of people being cured. Therefore, the number of people with the disease is still rising.

4.3.5 The Committee heard that early treatment of people with chronic hepatitis C in the general population could potentially reduce the likelihood of the spread of infection and that this would lead to a better estimate of cost effectiveness than that demonstrated in the models, in which the effect of the spread of infection had not been considered.

4.3.6 The Committee considered that, although the predicted effectiveness of the treatment of mild disease in a clinical setting was not as high as the average efficacy seen in the clinical trials, this difference was not likely to affect the importance of the therapy or overall cost effectiveness.

4.3.7 The Committee discussed a recent change in the UK marketing authorisation for peginterferon alfa-2b for people with genotype 1 (and by extension, genotype 4) and low viral loads (less than 600,000 IU/ml). This change allows combination therapy to be stopped at 24 weeks rather than continue to 48 weeks. The Committee has not reviewed the clinical effectiveness evidence for this modification of the marketing authorisation, so is not able to comment specifically on it. However, the Committee did note the caution carried in the marketing authorisation regarding the possibility that there may be a lower rate of sustained viral response if treatment is limited to 24 weeks. Nevertheless, if the success rate for sustained viral response were not to be affected by the shortening of the treatment period, the Committee recognised that this regimen would be cost effective compared with the 48-week treatment.

4.3.8 The Committee considered that an important question was whether it is cost effective to treat immediately people who have mild chronic hepatitis C with peginterferon alfa plus ribavirin or to wait until their disease reaches the moderate stage ('watchful waiting'). The Committee disregarded the manufacturers' models, which they considered had not made the relevant comparison. The Committee understood that, if the rate of progression to moderate disease were sufficiently low, it might be better not to subject all people with mild disease to the side effects of combination therapy because few might progress to moderate disease or beyond.

4.3.9 The Committee discussed the progression rates (from mild to moderate disease). The Committee was told that there is no way of knowing which patients are likely to progress from mild disease to moderate disease, but that progression is somewhat slower for younger people, for those who have been infected for a shorter time, for females and for certain ethnic groups. The Committee considered at length the progression rates assumed in the assessment report model, and noted that these were from clinical trials of people who presented for treatment. The Committee appreciated that this may represent a small proportion of the total number thought to be infected with

HCV and that people who were asymptomatic and had not sought treatment may experience a different rate of progression, on average, from those who had sought treatment. The Committee accepted that low rates of progression would mean that treating people with mild disease may affect the overall cost effectiveness of early treatment when compared with watchful waiting. The Committee considered that although low progression rates may exist among the population of all people with mild disease, it was likely that the progression rates found in clinical studies and used in the cost-effectiveness analysis might only be applicable to people with mild disease who present for treatment. Therefore, the Committee concluded that the estimated ICERs in the clinical setting currently pertaining in England and Wales would be acceptable.

4.3.10 However, the Committee recognised that if a much higher proportion of people with mild disease were to be diagnosed (for example, from a screening programme), the average progression rate of such a group could be so low that it might no longer be optimal to offer early treatment. That is, the Committee considered that the cost effectiveness of treating all people with mild disease identified as a result of a screening programme has yet to be proven, and that this guidance to treat people with mild disease might not necessarily apply to a screened population.

4.3.11 The Committee considered estimates used in the economic models of improvements in quality of life for people receiving treatment for mild disease and whether these improvements were importantly different between mild and moderate disease. The Committee heard that many people infected with chronic hepatitis C believe that they are stigmatised and discriminated against, which further reduces their quality of life. Clearing the disease could thus be associated with improvements that may not be reflected in economic models, and this could lead to an underestimate of the benefits of treatment. The Committee was persuaded that the estimated ICERs for combination therapy or monotherapy with peginterferon alfa for mild disease remained below £26,000 per QALY even if only very small improvements in quality of

life (1%) were considered. This was the same for all genotypes. The estimated ICER could be as high as £42,000 per QALY for genotype 1 (the genotype with the highest estimated ICER) only when there was assumed to be no improvement in quality of life when mild disease was cleared. The Committee was not persuaded that this latter scenario was appropriate, so accepted the range of predicted ICERs less than £26,000 per QALY.

4.3.12 The Committee was persuaded by the experts that the previous guidance (TA 75) on treating people with moderate chronic hepatitis C who continue to use intravenous drugs and/or misuse alcohol and people co-infected with HIV should be extended to members of all such groups who have mild disease. Thus, the Committee concluded that, with respect to those continuing to use intravenous drugs, in naturalistic settings, the rate of discontinuation of treatment would not be so great as to prevent the treatment being cost effective. In addition, with respect to people who continue consuming alcohol, the Committee considered that continued alcohol consumption is not in itself an absolute contraindication to therapy, but it should be emphasised as an important contributory factor to the development of liver disease and should be taken into account in advice and information given by the clinical team.

4.3.13 The Committee was mindful that the guidance on recommending treatment for mild disease caused by all genotypes would mean that liver biopsy will no longer be required to diagnose the severity of the disease before treatment can be initiated. It was felt that this would increase the uptake of treatment among people unwilling to undergo this procedure. Additionally, it would reduce the cost of disease management somewhat and avoid the pain and complications associated with liver biopsy. However, the Committee heard from a clinical expert that the number of biopsies carried out in people with chronic hepatitis C may not fall a great deal because biopsies would still be recommended for reasons not directly related to the decision to initiate therapy.

4.3.14 Treatment with combination peginterferon therapy has side effects, and the Committee appreciated that some people with mild disease may decide, in consultation with their clinician, to wait until they reach the moderate stage of the disease before beginning treatment. The Committee understood that, although people opting to begin treatment with combination therapy immediately may not need a liver biopsy, the situation may be different for people who opt to defer therapy. Clinicians will need to discuss the possible need for liver biopsy with people who opt to defer treatment. It should be explained that biopsy is used to determine whether a person has progressed to the moderate stage of the disease.

4.3.15 The Committee decided that the previous guidance on moderate or severe disease (TA 75) should be retained for mild disease with respect to: the length of treatment for different genotypes; people requiring monotherapy; and second courses of treatment. The Committee did not believe that there was sufficient 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.

5 Implementation

5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in ‘Standards for better health’ issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.

5.2 'Healthcare Standards for Wales’ was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by

Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 which requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.

5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TA106).

- Costing report and costing template to estimate the savings and costs associated with implementation.
- Audit criteria (see appendix C).

6 Recommendations for further research

6.1 Research is needed on the quality of life and progression rates among a random sample of people with mild disease compared with people presenting for treatment. This research might also include retrospective studies of progression among people who have already been diagnosed for reasons other than having symptoms of the disease.

7 Related guidance

7.1 NICE has issued the following related technology appraisal guidance.

- Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B. *NICE technology appraisal guidance* no. 96 (2006). Available from: www.nice.org.uk/TA096
- Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C. *NICE technology appraisal guidance* no. 75 (2004). Available from: www.nice.org.uk/TA075

8 Review of guidance

8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

8.2 This technology appraisal and TA 75 will be considered together for review in November 2007.

Andrew Dillon
Chief Executive
August 2006

Appendix A. Appraisal Committee members and NICE project team

A. Appraisal Committee members

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets twice a month except in December, when there are no meetings. The Committee membership is split into two branches, with the chair, vice chair and a number of other members attending meetings of both branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

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

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

Dr Jane Adam
Radiologist, St George's Hospital, London

Professor A E Ades
MRC Senior Scientist, MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol

Dr Tom Aslan
General Practitioner, Stockwell, London

Professor David Barnett (Chair)
Professor of Clinical Pharmacology, University of Leicester

Mrs Elizabeth Brain

Lay Member

Dr Richard Cookson

Senior Lecturer in Health Economics, School of Medicine Health Policy and Practice, University of East Anglia

Mrs Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Professor Christopher Eccleston

Director, Pain Management Unit, University of Bath

Dr Paul Ewings

Statistician, Taunton and Somerset NHS Trust, Taunton

Professor Terry Feest

Professor of Clinical Nephrology, Southmead Hospital, Bristol

Professor John Geddes

Professor of Epidemiological Psychiatry, University of Oxford

Mr John Goulston

Director of Finance, Barts and the London NHS Trust

Mr Adrian Griffin

Health Outcomes Manager, Johnson & Johnson Medical

Ms Linda Hands

Consultant Surgeon, John Radcliffe Hospital, Oxford

Dr Elizabeth Haxby

Lead Clinician in Clinical Risk Management, Royal Brompton Hospital, London

Dr Rowan Hillson

Consultant Physician, Diabeticare, The Hillingdon Hospital, Uxbridge

Dr Catherine Jackson

Clinical Senior Lecturer in Primary Care Medicine, University of Dundee

Professor Richard Lilford

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

Dr Simon Mitchell

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Ms Judith Paget

Chief Executive, Caerphilly Local Health Board

Dr Katherine Payne

Health Economist, The North West Genetics Knowledge Park, The University of Manchester

Dr Ann Richardson

Lay Member

Professor Philip Routledge

Professor of Clinical Pharmacology, College of Medicine, University of Wales, Cardiff

Dr Stephen Saltissi

Consultant Cardiologist, Royal Liverpool University Hospital

Mr Mike Spencer

General Manager, Clinical Support Services, Cardiff and Vale NHS Trust

Dr Debbie Stephenson

Head of HTA Strategy, Eli Lilly and Company

Professor Andrew Stevens (Vice Chair)

Professor of Public Health, University of Birmingham

Dr Cathryn Thomas

General Practitioner, and Associate Professor, Department of Primary Care and General Practice, University of Birmingham

Dr Norman Vetter

Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff

Professor Mary Watkins

Professor of Nursing, University of Plymouth

Dr Paul Watson

Medical Director, Essex Strategic Health Authority

B. NICE Project Team

Each appraisal of a technology is assigned to a Health Technology Analyst and a Technology Appraisal Project Manager within the Institute.

Alastair Fischer

Health Technology Analyst, NICE project team

Janet Robertson

Technical Adviser, NICE project team

Alana Miller

Technology Appraisal Project Manager, NICE project team

Appendix B. Sources of evidence considered by the Committee

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

Shepherd J, Jones J, Hartwell D, et al. *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 The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, assessment report and the appraisal consultation document. Consultee organisations are provided with the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsors:

- Roche Products
- Schering-Plough

II Professional/specialist and patient/carer group:

- Action on Hepatitis C
- Association of Nurses in Substance Abuse
- British Association for the Study of the Liver
- British Society of Gastroenterology
- Children's Liver Disease Foundation
- Department of Health
- Haemophilia Alliance
- Haemophilia Society
- Hepatitis C Trust
- Hepatitis Nurse Specialist Forum
- Mainliners

- Royal College of General practitioners
- Royal College of Nursing
- Royal College of Physicians
- Transplant Support Network
- UK Coalition of people Living with HIV and AIDS
- Welsh Assembly Government

III Commentator organisations (without the right of appeal):

- British National Formulary
- Foundation for Liver Research (formerly the Liver Research Trust)
- Health Protection Agency
- MRC Clinical Trials Unit
- National Coordinating Centre for Health Technology Assessment
- National Public Health Service for Wales
- NHS Quality Improvement Scotland
- Southampton Health Technology Assessment Centre (SHTAC)

C The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the appraisal consultation document.

- Professor G Foster, clinical expert, nominated by the Haemophilia Society
- Mr C Gore, patient expert, nominated by the Hepatitis C Trust
- Mr J Morris, patient expert, nominated by the Haemophilia Society
- Mr P Maulayah, clinical expert, nominated by the Hepatitis Nurse Specialist Forum

Appendix C. Detail on criteria for audit of the use of peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C

Possible objectives for an audit

An audit on the use of peginterferon alfa and ribavirin in the treatment of mild chronic hepatitis C could be carried out to ensure that the therapy is used appropriately.

Possible patients to be included in the audit

An audit could be carried out on a reasonable number of people being treated for mild chronic hepatitis C. Because 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 who have had a liver transplant, these people should be excluded from this audit. Where a large number of people are being treated, a representative sampling strategy is suggested.

Measures that could be used as a basis for an audit

The measures that could be used in an audit of peginterferon alfa and ribavirin in the treatment of mild chronic hepatitis C are as follows.

Criterion	Standard	Exception	Definition of terms
1. A person with mild chronic hepatitis C is treated with combination therapy comprising peginterferon alfa-2a and ribavirin or peginterferon alfa-2b and ribavirin, within their licensed indications	100% of people with mild chronic hepatitis C who present for treatment	A. If a woman is pregnant or breastfeeding B. If ribavirin is contraindicated or is not tolerated (see criterion 2)	For contraindications to ribavirin and symptoms of intolerance, see the summary of product characteristics.
2. A person with mild chronic hepatitis C who is unable to tolerate or has a contraindication to ribavirin is treated with monotherapy with peginterferon alfa-2a or peginterferon alfa-2b, within their licensed indications	100% of people with mild chronic hepatitis C who are unable to tolerate or have a contraindication to ribavirin and who present for treatment	None	For contraindications to ribavirin and symptoms of intolerance, see the summary of product characteristics.
3. A person with mild chronic hepatitis C makes the decision on immediate treatment with combination therapy or monotherapy or waiting until the disease has reached a moderate stage after fully informed consultation with the responsible clinician	100% of people with mild chronic hepatitis C who present for treatment	None	'Waiting until the disease has reached a moderate stage' can be referred to as 'watchful waiting.' Clinicians will need to agree on how the patient's decision and the fully informed consultation with the responsible clinician are documented, for audit purposes. The patient should understand that liver biopsy to determine the stage of the disease is not required if treatment is initiated immediately but

			biopsy may be recommended by the clinician for other reasons or if treatment is delayed.
4. For a person with mild chronic hepatitis C who has been treated with a first course of either combination therapy or monotherapy with peginterferon alfa and who has not had an early response, second or subsequent courses of treatment are provided.	0% of people with mild chronic hepatitis C who have had combination therapy or monotherapy with peginterferon alfa but who have not had an early response	None	'Early response' is as defined in the above measures, that is, the person's viral load has fallen to less than 1% of the initial level.

Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the } \textbf{criterion} \textbf{ ***plus*** } \text{number of patients who meet any } \textbf{exception} \text{ listed}}{\text{Number of patients to whom the } \textbf{measure} \text{ applies}} \times 100$$

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.