NHS

National Institute for Clinical Excellence

Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C

This guidance is a review and extension of Technology Appraisal Guidance No. 14 issued in October 2000.

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.

Technology Appraisal 75
January 2004

Technology Appraisal Guidance 75

Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment for chronic hepatitis C

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This document, which contains the Institute's full guidance for this appraisal, is available from the NICE website (www.nice.org.uk/TA075guidance).

An abridged version of this guidance (a 'quick reference guide') is also available from the NICE website (www.nice.org.uk/TA075quickrefguide). Printed copies of the quick reference guide can be obtained from the NHS Response Line: telephone 0870 1555 455 and quote reference number N0427.

Information for the Public is available from the NICE website or from the NHS Response Line (quote reference number N0428 for a version in English and N0429 for a version in English and Welsh).

The quick reference guide has been distributed to the following:

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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 available evidence. Health professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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This guidance is a review and extension of Technology Appraisal Guidance No. 14 issued in October 2000.
The Institute reviews each piece of guidance it issues. The review and re-appraisal has resulted in an extension to the guidance: combination therapy with pegylated interferon alfa and ribavirin is recommended for the treatment of people aged 18 years and over with moderate to severe chronic hepatitis C.

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 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.~~

This part-recommendation has been updated and replaced by NICE technology appraisal guidance 200.

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.

Recommendation 1.4 still applies for people who are treated with standard courses of combination therapy, but has been replaced by NICE technology appraisal guidance 200 (TA200) for people who are eligible for shortened courses of combination therapy (as described in recommendation 1.2 of TA200).

- 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:

This part-recommendation has been updated and replaced by NICE technology appraisal guidance 200.

- ~~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.

2 Clinical need and practice

2.1 Chronic hepatitis C (CHC) is a disease of the liver caused by the hepatitis C virus (HCV). Generally, the virus is transmitted by blood-to-blood contact. Before the introduction of screening in 1991 it was also spread through blood transfusions. Before the viral inactivation programme in the mid-1980s it was also spread through blood products. HCV can be acquired by people who inject drugs through the sharing of needles. There is a small risk of infection associated with tattooing, electrolysis, body 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 is thought to increase the risk of transmission.

2.2 People are often asymptomatic after exposure to the virus, but about 20% will develop acute hepatitis; some of them will experience malaise, weakness and anorexia. Up to 85% of those exposed do not clear the virus and go on to develop CHC. Progression of the disease occurs over 20–50 years. About 5–30% of people initially infected will develop cirrhosis within 20 years and a small percentage of these are at high risk of developing hepatocellular carcinoma. One-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.

2.3 Six major genetic types of HCV have been identified. Genotype 1 (G1) is the most common in the UK, and is found in about 40–50% of cases. Genotypes 2 and 3 (G2/3) contribute another 40–50%, and genotypes 4, 5 and 6 constitute the remainder of about 5%. Response to treatment varies between different genotypes. G1 is relatively more common among people infected through blood products, and G2/3 is relatively more common among people who inject themselves with illicit drugs.

2.4 Many individuals with HCV infection do not display symptoms. However, non-specific symptoms, such as fatigue, irritability, nausea, muscle ache, anorexia, abdominal discomfort and pain in the upper right quadrant, have been reported even in the absence of secondary pathology. If cirrhosis develops, people may have severe symptoms and complications.

2.5 Estimates of prevalence for hepatitis C in England and Wales vary considerably. The extant NICE guidance (see Section 8.1) puts the figure between 200,000 and 400,000, whereas the Assessment Report suggests between 50,000 and 500,000. 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 injecting drug users.

2.6 About two-thirds of people with HCV infection are men, mainly because more men inject themselves with illicit drugs, but also because there are far more men than women with haemophilia.

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

2.8 The primary aim of treatment for people with CHC is to clear HCV (defined as undetectable HCV-RNA in the serum) for at least 6 months after treatment cessation, in order to improve quality of life for patients and reduce the risk of cirrhosis and hepatocellular carcinoma.

2.9 The diagnosis of hepatitis C causes considerable anxiety to people. It is generally accepted, though without formal trial evidence, that all people diagnosed with the condition should receive adequate advice and information from a healthcare professional with knowledge and experience in the field.

2.10 The current standard treatment for moderate and severe chronic HCV infection is combination treatment with interferon alfa and ribavirin, except for people who cannot tolerate ribavirin, when interferon alfa monotherapy is used (Section 8.1 references the NICE guidance that is replaced by this guidance). The precise antiviral mode of action of interferon alfa is unknown. However, it appears to alter host-cell metabolism. It is available in the UK in two forms, interferon alfa-2a (Roferon A, Roche) and interferon alfa-2b (Viraferon, Schering-Plough).

2.11 Interferon alfa is eliminated from the body rapidly, having a plasma half-life of only about 4 hours. To maintain effectiveness against HCV, doses must be administered by injection on a minimum of 3 days a week.

2.12 The duration of monotherapy treatment is 48 weeks. For monotherapy, more than half of people who clear the virus after treatment relapse within 6 months of treatment cessation, but for those who remain clear after 6 months, about 90% remain so after 6 years. Thus, for this group, treatment may be called a cure. The dosage for interferon alfa treatment is usually 3 million units three times per week by subcutaneous injection. Injections are administered by clinical staff or by the patient after adequate training. People who respond usually do so within 12–16 weeks. Those who respond continue with this dose of interferon alfa for 48 weeks.

2.13 Many, but not all, people find interferon alfa therapy very hard to tolerate. After each injection, they may suffer influenza-like symptoms, and up to one-half of all people treated suffer from fatigue, headaches, pyrexia (fever), myalgia (aches and pains), insomnia and/or nausea. About one-quarter suffer hair loss, arthralgia (pain in the joints), rigors, irritability, pruritus (itching), depression, dermatitis and/or decreased appetite. There are significant problems of dropout and non-adherence with treatment as a result. Dropout rates of 7–14% have occurred. Figures on adherence are more difficult to quantify.

2.14 In the late 1990s, combination treatment of interferon alfa and ribavirin commenced, following trials that showed that, although ribavirin alone showed no activity against HCV, the effect of the combination of ribavirin with interferon alfa was much enhanced compared with that of interferon alfa alone. Since the introduction of combination therapy, monotherapy is used only for people unable to tolerate ribavirin.

2.15 Ribavirin (Copegus, Roche; Rebetol, Schering-Plough) is a nucleoside analogue with a broad spectrum of antiviral activity against RNA viruses. It is licensed for use in combination with interferon alfa-2a or interferon alfa-2b for treatment of CHC in:

- adult patients with histologically proven, previously untreated CHC, without liver decompensation, who are positive for serum HCV-RNA and who have fibrosis or high inflammatory activity

- adult patients with CHC who have previously responded (with normalisation of ALT at the end of treatment) to interferon alfa but subsequently relapsed.

2.16 Ribavirin is administered orally, usually in divided doses (200 mg per capsule or tablet). The dosage varies according to the patient's weight. Regular monitoring of full blood count to detect haemolytic anaemia is needed in order to judge whether to reduce or cease ribavirin treatment.

2.17 Ribavirin is contraindicated in pregnancy and breastfeeding, in severe debilitating medical conditions (particularly of the heart, blood, kidneys and liver), in haemoglobinopathies and in the presence of autoimmune diseases or severe psychiatric conditions. It may also cause haemolytic anaemia, for which close monitoring is required and a reduction in dose or cessation of treatment may be necessary.

2.18 Adverse effects related to combination therapy are similar in type and frequency to those of interferon alfa monotherapy and include influenza-like symptoms (fatigue, headache and fever), decreases in haematological parameters (neutrophil, white blood cell and platelet counts), gastrointestinal complaints (anorexia and nausea), dermatological symptoms (alopecia) and psychiatric disturbances (depression and anxiety). The trials indicate that discontinuation of treatment is more frequent (10–20%) for combination therapy than for monotherapy. Studies of combination therapy show that haematological events were the most common reason for either study withdrawal or dose reduction.

2.19 Standard treatment with interferon alfa combination therapy is either for 24 weeks (for people with G2/3) or for 48 weeks (for people with G1).

2.20 Treatment with interferon alfa monotherapy or combination therapy is not licensed for people younger than 18 years of age.

2.21 The following factors affect the efficacy of treatment.

- Genotype of the virus. This is the most important determinant of efficacy of treatment.

- High viral load. The higher the viral load, the lower the proportion of people with HCV who have a sustained virological response (SVR), all other things being equal. High viral load is the second most important determinant of efficacy of treatment.

- Age. Younger people fare better than older people. This may be because older people tend to have been infected for longer, although there appears to be an independent factor beyond that.

- The period between infection and treatment. Longer delays appear to adversely affect the efficacy of treatment.

- Weight. People who weigh more than the average have a lower response rate to treatment than those who weigh less than the average, when the dosages of interferon alfa (and ribavirin for combination therapy) are fixed.

- Fibrosis and cirrhosis of the liver (which act as markers for the damage done by the virus). The greater the damage, the less likely it is that the body can rid itself of the virus.

- The pre-treatment ALT level. The higher the pre-treatment ALT level, the lower the probability of treatment success.

- Racial group. Studies in the USA have shown that black people had a poorer response to treatment than white people, but there is no evidence of the impact of ethnicity in a UK setting.

- Gender. Women respond somewhat better than men to fixed doses (though evidence suggests that this may be due to women's lower average weight, and hence to the effective dose per kilogram).

2.22 Because HCV and HIV share common routes of transmission, many people with HIV are also infected with HCV. In these people, hepatitis C is a leading cause of death. It appears that HIV is associated with an acceleration of liver disease caused by HCV. Treatment of co-infected people is complicated by the possibility of adverse drug interactions, particularly with ribavirin. Studies show that treatment of people co-infected with HIV and HCV with interferon alfa combination therapy results in worthwhile (if somewhat lower) clearance rates of HCV than in people with HCV but not HIV. This is likely to be attributable to higher discontinuation rates and problems of drug interactions.

2.23 A 4-week cycle of interferon alfa at 3 million units three times a week costs around £200. Ribavirin for the same period costs from about £350 to £500. (All prices exclude VAT, *British National Formulary* 45th edition.) Therefore, 24 weeks of combination therapy of interferon alfa plus ribavirin will cost around £4000 (excluding monitoring costs). The cost of

treatment depends on which of interferon alfa-2a or interferon alfa-2b is used, and on weight, because the accompanying ribavirin dose is differentially weight-related.

2.24 The value of triple therapy (combination therapy of interferon alfa and ribavirin plus amantadine) has to be fully assessed.

3 The technology

3.1 Two product licences for a new form of interferon alfa, pegylated interferon alfa (called peginterferon alfa), have now been granted, both for use as monotherapy and for combination therapy with ribavirin in adults with hepatitis C. The pegylated form of interferon alfa contains an essentially inert 'tail', the function of which is to slow down the rate at which the body eliminates the molecule, enabling dosing to be less frequent. Of the two forms of pegylated interferon, peginterferon alfa-2a has a 40 kD branched chain polyethylene glycol molecule attached to the interferon with a stable bond. Peginterferon alfa-2b has a linear 12 kD polyethylene glycol chain that is attached via an unstable bond that breaks down in solution, releasing interferon alfa-2b.

3.2 Ribavirin doses for combination therapy are as follows. In conjunction with peginterferon alfa-2a (as for interferon alfa-2a), people who have HCV genotype 1 or 4 (and usually those who have genotype 5 or 6) and who weigh less than 75 kg take 1000 mg daily of ribavirin in divided doses. People who weigh more than 75 kg take 1200 mg ribavirin daily in divided doses. For people with HCV genotype 2 or 3 (and less usually those who have genotype 5 or 6) the dose of ribavirin is 800 mg daily in divided doses. In conjunction with peginterferon alfa-2b (as for interferon alfa-2b) and regardless of genotype, people who weigh less than 65 kg take 800 mg of ribavirin daily in divided doses, people who weigh 65–85 kg take 1000 mg daily in divided doses, and people who weigh more than 85 kg take 1200 mg daily in divided doses.

3.3 Peginterferon alfa has a much longer plasma half-life (50–130 hours for peginterferon alfa-2a and about 40 hours for peginterferon alfa-2b) than interferon alfa. It therefore needs to be injected only once per week, and the aggregate dose per month can be lower than for interferon, reducing most side effects. However, data show a higher incidence of neutropenia and thrombocytopenia for peginterferon alfa as either monotherapy or combination therapy than for the corresponding treatment regimen with interferon alfa. These adverse events may be managed by dose reduction.

3.4 For people who are considered for peginterferon alfa combination therapy, standard haematological tests and blood chemistry (full blood count and differential platelet count, liver function tests, uric acid, serum bilirubin, serum creatinine, and electrolyte concentrations) are necessary for all people before initiating therapy. The HCV genotype is also determined and baseline viral load established. Liver biopsy is undertaken, if there are no increased risks, in order to assess liver scarring and necro-inflammation according to an accepted severity scale. This is important in determining the need for treatment for people with significant fibrosis and necro-inflammation. People are seen weekly for 4 weeks, and then monthly during treatment, to check for side effects such as haemolysis, neutropenia, thyroid changes, depression and retinopathy.

3.5 Both peginterferon alfa-2a and alfa-2b are administered once a week by subcutaneous injection. The dose for peginterferon alfa-2a is 180 µg for either monotherapy or combination therapy. The dose for peginterferon alfa-2b is 1.5 µg per kg body weight (combination therapy), and either 0.5 µg or 1.0 µg per kg body weight (monotherapy).

3.6 Substituting peginterferon alfa for interferon alfa increases the 4-week cost of the interferon component from about £200 to about £550. Thus, a 24-week course of combination therapy with peginterferon alfa will cost about £6000. For monotherapy, the 24-week costs for interferon alfa and peginterferon alfa are about £1200 and £3200, respectively. The cost of a 48-week course is double that of a 24-week course. (All prices exclude VAT, *British National Formulary* 45th edition.) Costs may vary in different settings because of negotiated procurement discounts.

3.7 In pregnant or breastfeeding women, treatment with peginterferon alfa is contraindicated. Treatment with ribavirin is also contraindicated for these groups. For full details of side effects and contraindications of peginterferon alfa and of ribavirin, see the Summary of Product Characteristics.

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 The standard measurement of effectiveness of treatment of CHC is the virological response rate sustained for 6 months, called the SVR. SVR has been shown to closely reflect biopsy and ALT results taken from the same people at the same time.

4.1.2 Peginterferon alfa combination therapy versus interferon alfa combination therapy

4.1.2.1 The effectiveness of peginterferon alfa and ribavirin combination therapy, compared with interferon alfa and ribavirin combination therapy, for patients being treated with interferon alfa or peginterferon alfa for the first time has been investigated in two randomised controlled trials (RCTs) lasting 48 weeks. One trial used ribavirin and peginterferon alfa-2a (n = 1121) and the other used ribavirin and peginterferon alfa-2b (n = 1530). The results were broadly similar. For the first trial, peginterferon alfa-2a in combination with ribavirin yielded an SVR of 56% versus 44% for interferon alfa-2b in combination (95% confidence interval [CI] on the difference of 12 percentage points is 5 to 19 percentage points). In the second trial, the intention-to-treat analysis (which included patients taking ribavirin at lower than the licensed dose) of peginterferon alfa-2b in combination with ribavirin, the SVR was 54% versus 47% for interferon alfa-2b in combination (95% CI on the difference of 7 percentage points is 0.4 to 12.7 percentage points). In this arm of the study, all patients received 800 mg of ribavirin with 1.5 µg per kg body weight of peginterferon alfa-2b. The effect of ribavirin dose adjusted according to body weight was analysed in a subset of 188 of these patients. In this sub-population, the SVR for peginterferon alfa-2b in combination was 61% versus 47% for interferon alfa-2b in combination (95% CI on the difference of 14 percentage points is 5 to 22 percentage points). The licence for peginterferon alfa-2b combination therapy is based on this weight-adjusted ribavirin dosage. The Assessment Report recognises that the treatments with peginterferon alfa-2a and alfa-2b (both in combination with ribavirin) may be different and that there are differences between the trial

populations. However, it shows that, if the results of the trials of these two treatments are pooled, peginterferon alfa combination therapy yields an SVR of 56% on an intention-to-treat basis, whereas the interferon alfa combination yields an SVR of 47% on the same basis. The difference (9 percentage points) has a 95% CI from 5 to 13 percentage points. A second trial of peginterferon alfa-2a combination therapy has so far been reported in abstract form only. It extends the knowledge gained from the first trial by comparing different doses of ribavirin and lengths of treatment. Broadly, it confirms the results of the first trial using peginterferon alfa-2a. (Further results are currently commercial-in-confidence.)

4.1.2.2 The SVR in each of the two fully reported trials varied with both the baseline viral load and the genotype of the HCV. When there were more than 2 million copies of the virus in each millilitre of a patient's blood, the SVR was significantly lower than when there were fewer than 2 million copies. This was true for both arms of both of the trials.

4.1.2.3 SVRs for patients infected with HCV G1 are much lower than those for G2/3, whereas SVRs for genotypes 4, 5 and 6 (when they are known) appear to be between those of the more prevalent genotypes. For G1, SVRs for peginterferon alfa-2a combination therapy were 46%, compared with 36% for interferon alfa-2a combination therapy. When peginterferon alfa-2b combination therapy and interferon alfa-2b combination therapy were compared, the SVR values were 42% and 33%, respectively, on an intention-to-treat basis. On a weight-based ribavirin dosage, they were 48% and 34%, respectively. For G2/3, the SVR for peginterferon alfa-2a combination therapy was 76%, compared with 61% for the interferon alfa-2a therapy. When the peginterferon alfa-2b and interferon alfa-2b combination therapies were compared, the SVR values were 82% and 79%, respectively, on an intention-to-treat basis. On a weight-based ribavirin dosage, they were 88% and 80%, respectively.

4.1.2.4 Patients infected with HCV G2/3 respond to combination treatment with peginterferon alfa-2a in 95% of cases or more, and in about 80% of cases the response is sustained 6 months after treatment has finished. These rates are achieved after 24 weeks of treatment and are not increased by prolonging treatment for a further 24 weeks. For G1, however, the SVR after 48 weeks of treatment is much higher than that for 24 weeks of treatment, even though it is of the order of only 40–50%. This pattern follows that of combination therapy with interferon alfa-2a and interferon alfa-2b.

4.1.2.5 After 12 weeks of treatment, the viral load in people who eventually have an SVR after 24 or 48 weeks' treatment is generally reduced by a factor of 100 or more. That is, for every 1000 copies of the virus in the blood at the beginning of treatment, there would be 10 or fewer copies at the end of 12 weeks' treatment. This is known as a 2-log reduction.

4.1.2.6 For patients infected with HCV G2/3, more than 99% will respond with a 2-log reduction at 12 weeks. About 80% will eventually have an SVR. Of the very small number of patients not responding at 12 weeks, very few (perhaps less than 0.5% of the group that started treatment) have an SVR. For genotypes 1, 4, 5 and 6 (together called G1+), only 70–80% have a 2-log reduction at 12 weeks and, of these, about 60% (40–50% of the total group) have an SVR. Of the 20–30% that are non-responders at 12 weeks, few (perhaps 0.5% of those originally treated) go on to have an SVR.

4.1.2.7 Data from a subgroup of people with cirrhosis or bridging fibrosis and G2/3 in a recent trial of peginterferon alfa-2a, details of which are still confidential until its full publication, suggest that treatment beyond 24 weeks does not result in an increase in the SVR.

4.1.3 Peginterferon alfa monotherapy versus interferon alfa monotherapy

4.1.3.1 The Assessment Report found four RCTs that compared peginterferon alfa monotherapy with interferon alfa monotherapy. Three of these trials, involving about 960 people, were conducted with peginterferon alfa-2a, and one trial, involving more than 1200 people, was conducted with peginterferon alfa-2b. SVRs were much lower than for combination therapy. Peginterferon alfa-2a yielded a 36% pooled response, compared with 14% for interferon alfa-2a, whereas the SVR values for peginterferon alfa-2b versus interferon alfa-2b were 23% and 12%, respectively. Different doses of peginterferon alfa were used in three of the four trials, which occurred at different stages of drug development. All trials were 48 weeks in duration; hence the shorter treatment possibility for G2/3 was not tested.

4.1.4 Re-treatment of non-responders

4.1.4.1 The Assessment Report found 10 RCTs, involving some 860 people, that compared interferon alfa combination therapy with interferon alfa monotherapy for the re-treatment of non-responders to interferon alfa monotherapy. Of those re-treated with monotherapy, only 7 out of 413 had a virological response at the end of the trial, whereas for combination therapy, 53 out of 449 had such a response. For studies including both failure to respond and relapses from previous monotherapy, there were 16 responses out of 323 for monotherapy, compared with 75 out of 330 for combination therapy. The differences between the success rates for monotherapy compared with combination therapy are marked, although the percentage of successes when re-treating people failing to respond to monotherapy with combination therapy is only of the order of 10%.

4.1.4.2 Data for re-treatment with peginterferon alfa combination therapy for people previously treated with interferon alfa monotherapy or combination therapy is still tentative.

4.1.5 Adherence

4.1.5.1 Three studies (one published and one unpublished study of peginterferon alfa combination therapy, and one study of peginterferon alfa monotherapy) have retrospectively examined satisfactory adherence, defined as adhering to the designated dosing pattern at least 80% of the time. All studies show that SVR is significantly higher among people with G1 who show satisfactory adherence. For people with G2/3, one of the three studies also shows that SVR is significantly higher among those with satisfactory adherence.

4.1.6 Other patient subgroups: haemophilia

4.1.6.1 Many people with haemophilia were infected by blood products, in most cases by HCV G1. Many cases of G1 did not respond to monotherapy, or relapsed within 6 months. Small studies showed that a small but significant proportion of these relapses and treatment failures responded to peginterferon alfa combination therapy.

4.1.7 Other patient subgroups: HIV comorbidity

4.1.7.1 It is not unusual for people with HCV to be co-infected with HIV, because of their common transmission routes. Several patient submissions, one manufacturer and the Assessment Report examined this set of circumstances.

4.1.7.2 In people infected with both viruses, the rate of progression of CHC is much faster.

4.1.7.3 Several small trials have been conducted, all involving interferon alfa-2b, which show that the SVRs are of the order of 30% lower (for example, 35% instead of 50%) for people co-infected with HIV than for those without HIV.

4.1.7.4 There is no evidence that interferon alfa interacts with drugs taken for HIV, but there is evidence that ribavirin could do so when taken with peginterferon alfa, and may prove toxic. Additional care is called for when monitoring people receiving medication for HIV co-infection.

4.1.8 Other patient subgroups: injecting drug users

4.1.8.1 Current injecting drug users can have high rates of discontinuation in trials, and thus do not achieve success rates in trials with interferon alfa therapy as high as those obtained by other participants. However, there is evidence that where adherence is achieved, success rates are not significantly different.

4.1.9 Other patient subgroups: people with continued alcohol consumption

4.1.9.1 Alcohol consumption of more than 7 units per week not only increases liver damage for those infected with HCV, but also adversely affects its treatment.

4.1.10 Other patient subgroups: liver transplants

4.1.10.1 People with CHC who require a liver transplant usually develop the disease in the new liver. Very limited data (six people) showed that four people responded to peginterferon alfa-2b combination therapy.

4.1.11 Other patient subgroups: age, gender and ethnicity

4.1.11.1 Some differences have been observed in the success of treatment between people of different ages, between men and women, and between people of different ethnicity. These differences are relatively small compared with those resulting from viral genotype or viral load.

4.1.12 Other patient subgroups: mild CHC and acute hepatitis C

4.1.12.1 Trials in people with mild disease have not yet reported. Treatment of mild CHC is outside of the scope of this appraisal.

4.1.12.2 Acute infection is not covered by this appraisal. One trial has shown better clearance if HCV infection is treated immediately after onset, but it may not be possible to generalise its results to most people infected with HCV.

4.2 Cost effectiveness

4.2.1 Peginterferon alfa combination therapy versus interferon alfa combination therapy

4.2.1.1 The Assessment Report shows that peginterferon alfa combination therapy is a very cost effective intervention compared with interferon alfa combination therapy. For G2/3, given the very high sustained success rates at 24 weeks, treatment is cost effective at 24 weeks but not thereafter. For G1, 48-week treatment is cost effective compared with stopping therapy after 24 weeks. See Table 1.

Table 1: Cost effectiveness of combination therapy for different HCV genotypes

Comparison	Genotype	Treatment length (weeks)	Estimated incremental cost/QALY
(1) Peginterferon alfa combination vs interferon alfa combination	1	48	£4000 to £11,000
(2) Peginterferon alfa combination vs interferon alfa combination	4–6	48	£9000
(3) Peginterferon alfa combination vs interferon alfa combination	2–3	48	£7000 to £38,000
(4) Peginterferon alfa combination (24 weeks) vs peginterferon alfa combination (48 weeks)	Not 1	24 vs 48	£69,000 to negative benefits compared with 24 week treatment
(5) Peginterferon combination (24 weeks) vs peginterferon combination (48 weeks)	1	24 vs 48	£15,000 to £19,000 compared with 24 week treatment

Notes on Table 1: The estimated incremental cost/QALY figures were obtained from the Assessment Report using a modelling approach.

Rows (1) and (3): use data from the pivotal trials of peginterferon/interferon alfa-2a and of alfa-2b. The estimates differ because they are based on (a) different trials and (b) different doses of ribavirin.

Row (2): Uses data from the pivotal trial of peginterferon/interferon alfa-2b.

Rows (4) and (5): use data from an unpublished trial of peginterferon/interferon alfa-2a submitted in confidence by the manufacturer, for different doses of ribavirin. The genotype 'not 1' essentially refers to genotypes 2 and 3, as the numbers of those in genotypes 4, 5 and 6 were small.

4.2.1.2 In the Assessment Report, the estimates of incremental cost effectiveness ratios by viral genotype differ depending on the type of peginterferon alfa or interferon alfa and the dose of ribavirin. For G1, the estimated cost per quality-adjusted life year (QALY) gained of peginterferon alfa combination therapy compared with the corresponding interferon alfa combination therapy for 48 weeks' treatment ranges from £4000 to £11,000. For G2/3, the corresponding figures are £7000 to £38,000.

4.2.1.3 For monotherapy, all treatments are for 48 weeks (see Table 2).

Table 2: Cost effectiveness of monotherapy for different HCV genotypes

Comparison	Genotype	Estimated incremental cost/QALY
Peginterferon alfa monotherapy vs interferon alfa monotherapy	1	£19,000
Peginterferon alfa monotherapy vs interferon alfa monotherapy	2 and 3	£7000
Peginterferon alfa monotherapy vs interferon alfa monotherapy	4–6	£2000

Note on Table 2: The estimated incremental costs per QALY gained were obtained from the Assessment Report, based on a modelling approach using SVRs taken from a meta-analysis.

4.2.1.4 The manufacturers' models are similar in structure to that of the Assessment Report, and the estimates of cost effectiveness derived from them show even lower costs per QALY. In one instance, this can be explained in part by the longer time horizon (expected lifetime, as opposed to 30 years).

4.2.1.5 The Assessment Report shows that testing viral load at 12 weeks for G1+ and stopping treatment for people who do not exhibit a 2-log reduction in viral load is cost effective compared with continuing treatment. Some 20–30% of people infected with G1+ do not respond at 12 weeks, and

of these, less than 2% will eventually have an SVR. The cost per QALY gained from continuing treatment for the non-responders at 12 weeks is estimated to be £227,000. This is not the case for G2/3; there are very few non-responders at 12 weeks.

4.2.1.6 The cost effectiveness of treating with peginterferon combination therapy non-responders to interferon monotherapy has been estimated to be £3000 per QALY against no treatment. For non-responders to interferon combination therapy, it is £9000 per QALY against no treatment.

4.3 Consideration of the evidence

4.3.1 The Committee reviewed the evidence available on the clinical and cost effectiveness of treatment with interferon alfa and peginterferon alfa and ribavirin in CHC, having considered evidence on the nature of the condition and the value placed by users on the benefits of interferon and peginterferon alfa and ribavirin from people with CHC, 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 considered that peginterferon alfa combination therapy was both clinically and cost effective compared with interferon alfa combination therapy. Additionally, peginterferon alfa monotherapy was both clinically and cost effective compared with interferon alfa monotherapy. The Committee concluded that peginterferon alfa therapy should therefore supersede treatment using interferon alfa for all people unless particular side-effect considerations (neutropenia and thrombocytopenia risk) favour interferon alfa (without pegylation). The Committee also concluded that combination therapy should be used rather than monotherapy, except for people for whom ribavirin is contraindicated or cannot be tolerated.

4.3.3 The Committee gave careful consideration to the differential efficacy of treatment for patients infected with the different HCV genotypes. On the basis of the evidence reviewed, the Committee concluded that patients infected with HCV G2/3 should be considered differently from those with G1, and genotypes 4, 5 and 6 should be treated as for G1. For combination therapy, people with G2/3 should receive 24 weeks' treatment, whereas people with all other genotypes who have demonstrated a sufficient initial response should receive 48 weeks' treatment.

4.3.4 For combination therapy, the Committee discussed the requirement for testing for viral load at 12 weeks after the initiation of treatment as a means of assessing response. For G2/3, the number of non-respondents at this stage was such a small proportion that testing them to exclude further treatment was not considered cost effective. For all other genotypes, because the proportion of non-responders was much higher than for G2/3, the viral load response at 12 weeks is important to inform the need for treatment up to 48 weeks.

4.3.5 The Committee further considered the clinical and cost effectiveness of peginterferon alfa-2a versus peginterferon alfa-2b. Although it was aware that the two drugs had different dosage regimens and pharmacokinetic profiles, it considered that, in the absence of any head-to-head trials and on the basis of expert opinion received, the evidence was insufficient to recommend one of these products over the other. The Committee concluded that it would be important for clinicians to have the choice of either product in order to target different groups of people under particular clinical circumstances. The Committee, in this context, gave consideration to genotypes 2 and 3. The Committee noted that the SVRs for peginterferon alfa-2a were 15 percentage points above those for interferon alfa-2b, whereas for peginterferon alfa-2b, the SVRs were only 3 percentage points above those for interferon alfa-2b. However, the Committee considered the response of the former control group to be relatively low, whereas that of the latter control group was relatively high. It also noted that, when the weight-related dosage of ribavirin (on which the peginterferon alfa-2b licence is based) was considered, the relative efficacy of peginterferon alfa-2b compared with interferon alfa-2b was more marked. The Committee therefore considered that the apparent differences in response between the two forms of peginterferon for G2/3 should not result in a differential recommendation.

4.3.6 The Committee considered the use of peginterferon alfa for combination therapy in groups of people with HCV infection that were not represented in the pivotal clinical trials. These included people with haemophilia and people co-infected with HIV. The Committee concluded that, based on the evidence available, there was no reason to make any different provision for these groups. It did, however, note that there might be occasions where ribavirin may interact with medication for HIV, necessitating either a change in the latter or a switch to peginterferon alfa monotherapy.

4.3.7 For combination therapy, the Committee considered the differences in treatment efficacy for people of different age, gender and ethnicity, and decided that, where sufficient evidence existed, the efficacy differences were not great enough to give rise to a different recommendation for any of these subgroups.

4.3.8 The Committee heard that, although injecting drug users with HCV might, on average, seek treatment less frequently than other people with HCV, those who do seek treatment have similar adherence rates to other people with HCV. Furthermore, the evidence provided by the experts persuaded the Committee that current information indicated that HCV re-infection rates for people on interferon or peginterferon therapy were low in those who continue to inject illicit drugs. Thus, although rates of discontinuation of injecting drug users in trials have been high, the Committee was prepared to accept that in naturalistic settings, the rate of discontinuation would not be so great as to prevent the treatment being cost effective.

4.3.9 The Committee heard that continued alcohol consumption even at levels of intake much lower than the recommended maximum levels for the general population might be harmful for people with CHC-induced liver disease. This is because of the effect of alcohol on the progression of liver disease and also because alcohol reduces the efficacy of peginterferon/interferon alfa as therapy for CHC. The Committee considered that continued alcohol consumption was, however, not in itself an absolute contraindication to therapy but should be emphasised as an important factor to be taken into account in advice and information given by the clinical team.

4.3.10 The Committee carefully considered the situation of people who had already been treated with peginterferon or interferon alfa. Evidence shows that for those treated with interferon alfa monotherapy who had either not responded, or had responded but then relapsed, further treatment with combination therapy (with either peginterferon or interferon alfa) will be cost effective, although not as cost effective as for people not previously treated. The Assessment Group produced a further modelling analysis which assumed that re-treatment with peginterferon alfa combination, for those who had already undergone interferon alfa combination therapy, would yield an SVR equal to the difference between the SVRs of the two therapies. This analysis suggested that it could be cost effective to re-treat those previously treated with interferon alfa combination therapy who had relapsed

or who had not responded. The Committee, after also receiving expert clinical advice on this matter and recognising the great uncertainty surrounding these estimates, decided that these groups of people should be suitable for treatment. The Committee reached the same conclusion for the few, if any, people previously treated without sustained virological response with peginterferon alfa monotherapy. However, it decided that there was no clinical or modelling evidence, or expert opinion, to support re-treatment of people who had previously been treated with peginterferon alfa combination therapy.

4.3.11 For people unable to take ribavirin, the Committee decided that peginterferon alfa monotherapy should be the treatment of choice, because it is both clinically and cost effective compared with interferon alfa monotherapy, despite lower clearance rates of the virus than for combination therapy. All people taking peginterferon alfa monotherapy should receive treatment for 48 weeks, regardless of genotype, because it was noted that there is currently no evidence for the effectiveness of a shorter period (24 weeks) of treatment. The requirement for 12 weeks' viral load testing was also considered for this group, and it was concluded that it should apply to people with every HCV genotype. Although there was no direct evidence of the cost effectiveness for this recommendation, it could reasonably be assumed that viral testing at 12 weeks would be at least as cost effective as in combination therapy, and there was no evidence to support G2/3 being treated any differently from other genotypes. The provisos for combination therapy in Section 4.3.3 (except for the 24-week treatment for G2/3), and Sections 4.3.5 to 4.3.9, also apply to treatment with monotherapy.

4.3.12 The Committee considered the treatment of people classified on the basis of liver biopsy as having mild chronic CHC. It was aware that there were two trials of people with mild disease that would shortly be reporting. The correct and cost-effective management of this group was considered very important and, although people with mild disease represent a small subgroup of the current RCT evidence base, it was decided that waiting for the current specific trials to report would provide a more robust basis on which to provide guidance to the NHS.

4.3.13 The Committee discussed the question of the need for liver biopsy at some length. It concluded that, because the basis for the original guidance (see Section 8.1) required the definition of the extent of liver disease, the requirement for biopsy before deciding on appropriate therapy should remain. It was persuaded that alternative non-invasive tests of liver function could not currently be relied upon to act as appropriate surrogates for direct histological examination. However, the Committee considered that, in due course, the result of the trials in mild disease might affect this requirement. The Committee believed that there were grounds for making exceptions for people with haemophilia and risk of bleeding or with a previous adverse reaction to liver biopsy, and for those with extra-hepatic symptoms sufficient to merit treatment.

4.3.14 The Committee considered that the effective delivery of the guidance in Section 1 would be critically dependent on the existence of a properly structured clinical environment for people with CHC. Thus, it concluded that the decision to undertake therapy should only be initiated by a physician with specialist knowledge of the treatment of CHC. Additionally it is important that a clinical team including specialist nurses is available for lifestyle advice to facilitate the informed decision of the individual to undertake treatment and to help him or her successfully complete the course of therapy.

5 Recommendations for further research

5.1 Current trials involving peginterferon alfa for people with moderate or severe chronic CHC are reported in Appendix 11 of the Assessment Report. These consist of one trial of a triple therapy, five trials of combination therapy, two of monotherapy, five of co-infected populations and one to assess the long-term SVR in children. Trials for people with mild chronic CHC are also near completion. In addition, a randomised controlled trial of combination therapy involving pegylated interferon alfa-2a versus alfa-2b is being planned.

5.2 A well-constructed trial of peginterferon alfa combination therapy versus other therapies involving interferon alfa is needed in children with chronic CHC.

6 Implications for the NHS

6.1 The total budgetary impact of combination therapy depends on a number of factors: prevalence, proportion of people diagnosed, proportion of the people diagnosed who attend for assessment, and the proportion considered suitable for treatment, as well as the proportions who actually take up therapy and complete it. It also depends on whether peginterferon alfa combination treatment is being compared with interferon alfa combination therapy, peginterferon alfa or interferon alfa monotherapy, or no treatment.

6.2 Currently, only about 2000 people in England and Wales each year are being treated for HCV infection with some form of interferon or peginterferon alfa therapy. On the basis that all these people will eventually receive peginterferon alfa combination therapy, that the numbers being treated do not change with time, and that peginterferon alfa combination therapy costs about £3200 more per patient than interferon alfa combination therapy, the additional drug expenditure would be up to £6.4 million per year. However, it is likely first, that the number of people able to benefit from treatment (injecting drug users and people who have had an alcohol problem) will be increased as a consequence of this guidance, and second, that the number of people seeking treatment will increase as education about the condition increases and as people become aware of improvements in treatment. This would significantly increase drug expenditure.

6.3 Testing people with G1+ infection at 12 weeks and ending treatment for those who are not responding to therapy would cut the additional costs by about 16%, or about £1 million.

6.4 There will also be a re-treatment cost for non-responders to previous therapy. The numbers of people involved are not known with any degree of certainty. The following assumptions have been made:

- 1000 people have not had an SVR to monotherapy and have not subsequently been treated with a combination therapy
- 250 are still alive and would wish to undertake peginterferon alfa combination therapy
- 60% are G1+ and 40% are G2/3

- half of the people with G1+ respond after 12 weeks and are treated for 48 weeks at a cost of £12,000 each
- the other half of the people with G1+ are treated for 16 weeks at a cost of £4000 each
- the people with G2/3 are treated for 24 weeks at a cost of £6000 each
- the number of people who have been treated with previous interferon combination therapy but who have either not responded or have relapsed is 2000, of whom 75% (1500) are G1+ and 25% (500) are G2/3
- 1000 of the G1+ and 400 of the G2/3 seek re-treatment
- 25% of the G1+ group respond after 12 weeks and are treated for 48 weeks at a cost of £12,000 each; the 75% that does not respond are treated for 16 weeks
- the G2/3 group is treated for 24 weeks at a cost of £6000 each.

6.5 The drug cost, compared with no interferon treatment, would be approximately £1.8 million for people who have had previous monotherapy treatment and a further £8.4 million for people who have had previous combination therapy treatment. This is likely to be spread over about 2 years, equating to £5.1 million per year. The total increased drug cost for the next 2 years would therefore be about £10.5 million per year. Should people seeking re-treatment delay further treatment, the costs per year would be lower than £10.5 million per year, but would be spread over a longer time period.

6.6 This estimation procedure ignores other costs, such as the cost of testing for genotype and viral load, but also ignores the additional potential treatment offsets down the line.

7 Implementation and audit

7.1 Treatment for CHC should be provided by physicians who are expert and experienced in the diagnosis and management of viral hepatitis, and a clinical nurse specialist for hepatitis with access to supportive services including an accredited virology laboratory, a liver pathologist and a radiology department, consistent with Department of Health (2002) *Hepatitis C Strategy for England*. London: Department of Health.

7.2 All clinicians who care for people with CHC should review their current practice and policies to take account of the guidance set out in Section 1.

7.3 Local guidelines, protocols or care pathways that refer to the care of people with CHC should incorporate the guidance.

7.4 To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C.

7.4.1 An individual with moderate to severe CHC who is aged 18 years or older (except a woman who is pregnant or breastfeeding) is treated with peginterferon alfa and ribavirin combination therapy within licensed indications if he or she meets any one of the following.

7.4.1.1 The individual has not previously been treated with interferon alfa or peginterferon alfa.

7.4.1.2 The individual has been treated previously or is currently being treated with interferon alfa as monotherapy or combination therapy.

7.4.1.3 The individual has been previously treated with peginterferon alfa monotherapy only, and either responded at the end of treatment but subsequently relapsed, or was not responding at the end of treatment.

7.4.2 For an individual who meets the criteria in Section 7.4.1, treatment is carried out as follows.

7.4.2.1 If the individual is infected with HCV of genotypes 2 and/or 3, treatment is for 24 weeks.

7.4.2.2 If the individual is infected with HCV of genotypes 1, 4, 5 or 6, (or infected with more than one genotype including at least one of genotypes 1, 4, 5 or 6), initial treatment is for 12 weeks. If the viral load has been reduced to less than 1% of its level at the start of treatment, treatment is continued for 48 weeks. If the viral load exceeds 1% of its level at the start of treatment, treatment is discontinued.

7.4.3 An individual with moderate to severe CHC who is aged 18 years or older (except a woman who is pregnant or breastfeeding) for whom ribavirin is contraindicated or is not tolerated is treated with peginterferon alfa monotherapy. The individual is tested for viral load at 12 weeks of treatment. If the viral load has reduced to less than 1% of its

level at the start of treatment, treatment continues for a total of 48 weeks. If the viral load has not fallen to less than 1% of its level at the start of treatment, treatment is stopped at 12 weeks.

7.4.4 Before treatment is given, an individual has a liver biopsy to determine if the individual has moderate or severe CHC, except if the individual meets one of the following.

7.4.4.1 Liver biopsy poses a substantial risk to the individual.

7.4.4.2 The individual has symptoms of extra-hepatic HCV infection sufficient to impair quality of life.

8 Related guidance

8.1 This guidance is a review of and an extension to:

National Institute for Clinical Excellence (2000) Guidance on the use of ribavirin and interferon alpha for hepatitis C. *NICE Technology Appraisal* No. 14. London: National Institute for Clinical Excellence. Available from: www.nice.org.uk

9 Review of guidance

9.1 The use of this technology for mild CHC (and any consequent changes that this may have on this guidance) will be considered after the publication of the results of the two relevant clinical trials, and at the earliest in August 2004. The full guidance will be reviewed in November 2006.

Andrew Dillon
Chief Executive
January 2004

A version of this guidance written for people with chronic hepatitis C, and the public, is available from the Institute's website (www.nice.org.uk) and from the NHS Response Line (telephone 0870 1555 455 and quote reference number N0428 for a version in English only and N0429 for a version in English and Welsh).

Appendix A

Appraisal Committee members and NICE project team

A. Appraisal Committee members

NOTE 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

Dr Sunil Angris
General Practitioner, Waterhouses Medical Practice, Staffordshire

Dr Darren Ashcroft
Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

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

Dr Peter Barry
Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Professor John Brazier
Health Economist, University of Sheffield

Professor John Cairns
Professor of Health Economics, Health Economics Research Unit, University of Aberdeen

Professor Mike Campbell
Statistician, Institute of General Practice & Primary Care, Sheffield

Dr Mark Chakravarty
Head of Government Affairs and NHS Policy, Procter and Gamble Pharmaceuticals (UK) Ltd, Egham, Surrey

Dr Peter I Clark
Consultant Medical Oncologist, Clatterbridge Centre for Oncology, Wirral, Merseyside

Dr Mike Davies
Consultant Physician, University Department of Medicine & Metabolism, Manchester Royal Infirmary

Professor Jack Dowie
Health Economist, London School of Hygiene

Dr Paul Ewings
Statistician, Taunton & Somerset NHS Trust, Taunton

Ms Sally Gooch
Director of Nursing, Mid-Essex Hospital Services NHS Trust, Chelmsford

Professor Robert Kerwin
Professor of Psychiatry and Clinical Pharmacology, Institute of Psychiatry, London

Dr Stephen Saltissi
Consultant Cardiologist, Royal Liverpool University Hospital

Mr Miles Scott
Chief Executive, Harrogate Health Care NHS Trust

Professor Andrew Stevens (Vice-Chair)
Professor of Public Health, University of Birmingham

Professor Mary Watkins
Professor of Nursing, University of Plymouth

Dr Norman Waugh
Department of Public Health, University of Aberdeen

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.

Dr Alastair Fischer
Technical Lead,
NICE project team

Nina Pinwill (up to August 2003) and Dr Sarah Cumbers (from August 2003)
Project Managers,
NICE project team

Appendix B

Sources of evidence considered by the Committee

The following documentation and opinions were made available to the Committee:

A The Assessment Report for this appraisal was prepared by the Southampton Health Technology Assessment Centre (SHTAC), Wessex Institute for Health Research and Development, University of Southampton

I Shepherd J, Brodin H, Cave C, et al, *Pegylated interferon alpha 2a and 2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review*, 29 May 2003

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 Appraisal Consultation Document (ACD). Consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination.

I Manufacturer/sponsors:
- Roche Products Ltd
- Schering-Plough Ltd

II Professional/specialist and patient/carer groups:
- Action on Hepatitis C
- Association of Nurses in Substance Abuse
- British Association for Study of the Liver
- British Liver Trust
- British Society of Gastroenterology
- Department of Health and the Welsh Assembly Government
- Haemophilia Society
- Hepatitis C Trust
- Hepatitis Nurse Specialist Forum
- Mainliners
- Royal College of General Practitioners
- Royal College of Pathologists
- Royal College of Physicians
- Royal Pharmaceutical Society
- Terrence Higgins Trust
- UK Haemophilia Centre Doctors' Organisation

III Commentator organisations (without the right of appeal):

- National Hepatitis C Resource Centre
- NHS Quality Improvement Scotland

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 interferon alfa (pegylated and non-peglyated) and ribavirin in the treatment of chronic hepatitis C by attending the initial Committee discussion and/or providing written evidence to the Committee. They were invited to comment on the ACD.

- Dr Has Dasani, Physician for Haemophilia Centre, University Hospital of Wales, Cardiff
- Dr Graham Foster, Consultant Hepatologist, Queen Mary College, The Royal London Hospital
- Mr Charles Gore, Chief Executive, The Hepatitis C Trust
- Mr Robert James, Chair of Birchgrove, on behalf of The Haemophilia Society
- Dr Elizabeth McCruden, Senior Lecturer and Honorary Consultant Virologist, Institute of Virology, University of Glasgow and North Glasgow NHS University Trust
- John Morris, Hepatitis Worker and Robert James, Chair of Birchgrove, on behalf of The Haemophilia Society UK
- Professor Howard Thomas, Professor of Medicine, Department of Medicine, Imperial College at St Mary's Hospital, British Society of Gastroenterology

Appendix C

Detail on criteria for audit of the use of interferon alfa (pegylated and non-pegylated) and ribavirin in the treatment of chronic hepatitis C

Possible objectives for an audit

An audit on the use of pegylated and non-pegylated interferon alfa and ribavirin in the treatment of CHC could be carried out to ensure that combination 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 CHC, for audit purposes. If a large number of people is being treated, a representative sampling strategy is suggested.

Measures that could be used as a basis for audit

The measures that could be used in an audit of pegylated and non-pegylated interferon alfa and ribavirin in the treatment of CHC are as follows.

Criterion	Standard	Exception	Definition of terms
1. An individual with moderate to severe CHC and who is aged 18 years or older is provided with peginterferon alfa and ribavirin combination therapy within licensed indications if he or she meets one of the following: a. has not been treated previously with interferon alfa or peginterferon alfa **or** b. has been treated previously or is currently being treated with interferon alfa monotherapy or combination therapy **or** c. has been previously treated with peginterferon alfa monotherapy only and either responded at the end of treatment but subsequently relapsed, or who was not responding at the end of treatment	100% of individuals who meet one of a–c	A. Peginterferon alfa is contra-indicated; in particular, the patient is pregnant or breastfeeding B. Ribavirin is contraindicated or is not tolerated, in which case the individual is: 1) treated with peginterferon alfa monotherapy **and** 2) tested for viral load at 12 weeks of treatment **and** 3) treated for 48 weeks if the viral load has reduced to less than 1% of its level at the start of treatment **or** discontinued treatment if the viral load exceeds 1% of its level at the start of treatment	Pegylated interferon alfa includes peginterferon alfa-2a and peginterferon alfa-2b. 'Moderate to severe CHC' means there is histological evidence of significant scarring (fibrosis) and/or significant necrotic inflammation. See criterion 3 for exceptions for carrying out a liver biopsy for this purpose. Clinicians will need to agree locally on how to measure compliance with licensed indications, for audit purposes and will need to agree on how to define lack of response to treatment (for 1c) for audit purposes. For exception B, contraindications include: pregnancy, breastfeeding, the presence of severe debilitating medical conditions (particularly of the heart, blood, kidneys or liver), haemoglobinopathies, the presence of auto-immune diseases, severe psychiatric conditions, or haemolytic anaemia. For the exception, 'not tolerated' can include: influenza-like symptoms (fatigue, headache and fever), decreases in haematological parameters (neutrophil, white blood cell or platelet counts); gastrointestinal complaints such as anorexia or nausea, dermatological symptoms including alopecia, and psychiatric disturbances including depression or anxiety.

Criterion	Standard	Exception	Definition of terms
2. An individual who meets 1a–c above is treated as follows: a. for 24 weeks if the individual is infected with HCV of genotypes 2 and/or 3 **or** b. for 12 weeks if the individual is infected with CHC of genotypes 1, 4, 5 or 6 **and** for 48 weeks if the individual is infected with HCV of genotypes 1, 4, 5 or 6 and the viral load at 12 weeks has reduced to less than 1% of its level at the start of treatment **or** treatment is discontinued after 12 weeks if the individual is infected with HCV of genotypes 1, 4, 5 or 6 and viral load at 12 weeks exceeds 1% of its level at the start of treatment.	100% of individuals in 1a–c above	None	If an individual is infected with more than one genotype, including at least one of genotypes 1, 4, 5 or 6, treatment should follow 2b and c. 'Reduced to less than 1% of the level at the start of treatment' = at least a 2-log reduction
3. A liver biopsy is carried out on each individual receiving any kind of interferon therapy.	100% of individuals in 1a–c above	A. Liver biopsy poses a significant risk B. The individual has symptoms of severe extra-hepatic HCV infection sufficient to impair quality of life	For exception A, conditions include haemophilia and individuals who have experienced an adverse event after undergoing a previous liver biopsy. Clinicians will need to agree locally on how to define severe extra-hepatic HCV infection and quality-of-life impairment, for audit purposes.

Calculation of compliance

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

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

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.

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