Appendix A

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C (Part-review of TA75 and TA106)

Draft scope

Appraisal objective

To review, and update as necessary, the Institute's current guidance on the clinical and cost-effectiveness of peginterferon alfa and ribavirin for the treatment of chronic hepatitis C.

Background

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

People infected with HCV are often asymptomatic, but about 20% will develop acute hepatitis and 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 require liver transplantation.

There are 6 major genotypes and several sub-types of HCV, the prevalence of which varies geographically. In England and Wales, the most prevalent genotypes are 3a (37%), 1a (32%) and 1b (15%). Genotype is a key predictor of the effectiveness of anti-viral treatment and patients with genotypes 2 and 3 generally respond better to treatment than those with genotypes 1, 4, 5 and 6.

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 7,000 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.

A person is classified as having mild, moderate or severe chronic hepatitis C based on the extent of liver damage. The main indicator of liver damage is the

degree of fibrosis, although the degree of necroinflammation also contributes to the diagnosis.

For the majority of people with hepatitis C (regardless of disease severity), 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 (in line with NICE guidance TA75 and TA106). Specific NICE guidance for mild, moderate and severe hepatitis C is listed in the Appendix.

The technologies

Interferons (interferon alfa-2a and -2b / peginterferon alfa-2a and -2b)

Two forms of interferon alfa (interferon alfa-2a [Roferon-A, Roche Products] and interferon alfa-2b [IntronA, Schering-Plough]) and two forms of pegylated interferon alfa (peginterferon alfa-2a [Pegasys, Roche Products] and peginterferon alfa-2b [Viraferonpeg, Schering-Plough]) have marketing authorisations in the UK for adult patients with chronic hepatitis C. In all cases it is recommended that interferon or peginterferon is used in combination with ribavirin. Monotherapy with an interferon is only recommended for people who are unable to tolerate ribavirin, or for whom ribavirin is contraindicated.

Since TA075 and TA106 were published there have been extensions to the licences for the peginterferons as follows:

- Peginterferon alfa-2a
  - Extension of the therapeutic indication to include treatment in patients who previously did not respond to interferon (pegylated or non-pegylated) in combination therapy with ribavirin.
  - Option to shorten the treatment duration in patients with genotype 2 or 3 with a rapid viral response (defined as HCV RNA undetectable by week 4) from 24 weeks to 16 weeks.
  - Option to shorten the treatment duration in patients with genotype 1 with a low viral load and rapid viral response (defined as HCV RNA undetectable at week 4 and at week 24) and patients with genotype 4 and a rapid viral response from 48 weeks to 24 weeks
  - Update of posology section to include recommendations for people co-infected with HIV.
- Peginterferon alfa-2b
  - Extension of the therapeutic indication of peginterferon alfa-2b in combination with ribavirin to include treatment in patients who previously did not respond to interferon (pegylated or non-pegylated) in combination therapy with ribavirin or interferon monotherapy. Also update of the posology section regarding the lack of data to support the

re-treatment of non-responding patient with genotype 1 HCV for more than 48 weeks.

– Extension of the therapeutic indication in combination with ribavirin to include treatment in patients co-infected with HIV

For full details of the therapeutic indications, posology and method of administration see the relevant summary of product characteristics.

Ribavirin

Ribavirin (Copegus, Roche Products; Rebetol, Schering-Plough) is indicated for the treatment of chronic hepatitis C and must only be used as part of a combination regimen with peginterferon alfa or interferon alfa. Monotherapy must not be used.

There are differences in the licensed indications for the two products in that each is only licensed for use with the interferon products made by the same manufacturer.

Intervention(s)	• Combination therapy (peginterferon alfa and ribavirin) • Peginterferon alfa monotherapy (for those who cannot tolerate ribavirin)
Population(s)	Patients with chronic hepatitis C infection. The following groups will be considered: • people who have been previously treated with peginterferon alfa and ribavirin in combination • people who meet the criteria for receiving shortened courses of peginterferon alfa and ribavirin in combination • people with HCV/HIV co-infection

Comparators	For people who have been previously treated with peginterferon alfa and ribavirin in combination: • supportive care, including treatment without any form of interferon therapy For people who meet the criteria for receiving shortened courses of peginterferon alfa and ribavirin in combination: • standard-duration courses of peginterferon/ribavirin (up to 24 or 48 weeks as appropriate): For people with HCV/HIV co-infection: • supportive care, including treatment without any form of interferon therapy.
Outcomes	The outcome measures to be considered include: • virological response to treatment • sustained virological response • biochemical response (e.g. ALT) • histological improvement (inflammation and fibrosis) • survival • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation.

Related NICE recommendations	Related Technology Appraisals: Technology Appraisal 75 (Jan 2004), 'Interferon alfa and ribavirin for the treatment of chronic hepatitis C - part review of existing guidance no.14'. Technology Appraisal 106 (Aug 2006), 'Peginterferon alfa and ribavirin for the treatment of mild hepatitis C'.

Questions for consultation

Is it appropriate to limit this appraisal to the new indications only, or should the previous guidance be reviewed completely?

If it is appropriate only to include the new indications, are the populations and comparators defined appropriately?

Are there any subgroups of patients in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Is there a need for guidance on the use of interferon alfa-2b (with or without ribavirin) in children with hepatitis C? Would a separate appraisal for this indication be appropriate?

Appendix

TA75 – The use of interferon alfa, peginterferon alfa and ribavirin for the treatment of chronic hepatitis C

1.1. Combination therapy with peginterferon alfa and ribavirin is recommended within its licensed indications for the treatment of people aged 18 years and over with moderate to severe chronic hepatitis C (CHC), defined as histological evidence of significant scarring (fibrosis) and/or significant necrotic inflammation.

1.2. People with moderate to severe CHC are suitable for treatment if they have:

- not previously been treated with interferon alfa or peginterferon alfa, or
- been treated previously with interferon alfa (as monotherapy or in combination therapy), and/or
- previously received peginterferon alfa monotherapy only and responded at the end of treatment but subsequently relapsed, or did not respond at the end of treatment.

1.3. People currently being treated with interferon alfa, either as combination therapy or monotherapy, may be switched to the corresponding therapy with interferon alfa.

1.4. Treatment for the groups identified in Sections 1.1. and 1.2 should be as follows:

- people infected with hepatitis C virus (HCV) of genotype 2 and/or 3 should be treated for 24 weeks.
- for people infected with HCV of genotype 1, 4, 5, or 6, initial treatment should be for 12 weeks. Only people showing, at 12 weeks, a reduction in viral load to less than 1% of its level at the start of treatment (at least 2-log reduction, see Section 4.1.2.5) should continue treatment until 48 weeks. For people in whom viral workload at 12 weeks exceeds 1% of its level at the start of treatment, treatment should be discontinued.

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 discontinued for a total of 48 weeks. If viral load has not fallen to this extent, treatment should stop at 12 weeks.

1.6. People for whom liver biopsy poses a substantial risk (such as those with haemophilia, or those who have experienced an adverse event after undergoing a previous liver biopsy), and people with symptoms of extra-hepatic HCV infection sufficient to impair quality of life, may be treated on clinical grounds without prior histological classification.

1.7. There is insufficient evidence to recommend combination therapy using peginterferon alfa or interferon alfa in people who:

- have previously been treated with combination therapy using peginterferon alfa, and/or
- are younger than 18 years of age, and/or
- have had a liver transplantation. Treatment of CHC recurrence after liver transplantation (whether or not the person had been treated with interferon alfa or peginterferon alfa therapy at any time before transplantation) should be considered as experimental and carried out only in the context of a clinical trial.

TA106 – Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C

1.1 Combination therapy, comprising peginterferon alfa-2a and ribavirin or peginterferon alfa-2b and ribavirin, is recommended, within the licensed indications of these drugs, for the treatment of mild chronic hepatitis C.

1.2 Monotherapy with peginterferon alfa-2a or peginterferon alfa-2b is recommended, within the licensed indications of these drugs, for the treatment of mild chronic hepatitis C for people who are unable to tolerate ribavirin, or for whom ribavirin is contraindicated.

1.3 The decision on whether a person with mild chronic hepatitis C should be treated immediately or should wait until the disease has reached a moderate stage ('watchful waiting') should be made by the person after fully informed consultation with the responsible clinician. The decision to treat need not depend on a liver biopsy to determine the stage of the disease if treatment is initiated immediately. However, a biopsy may be recommended by the clinician for other reasons or if a strategy of watchful waiting is chosen.

1.4 The duration of treatment should vary according to the licensed indications of the chosen drug, the genotype of the virus, the initial viral load, the response to treatment, and the treatment regimen chosen.

1.5 Second or subsequent courses of treatment are not recommended for people who have been treated with a first course of either combination

therapy or monotherapy with peginterferon alfa if they have not had an early response (as indicated by reduction in viral load at 12 weeks).

1.6 There is insufficient evidence to recommend combination therapy or monotherapy with peginterferon alfa for people with mild chronic hepatitis C who are under the age of 18 years, or those who have had a liver transplant.