pegylated interferon α 2b (ViraferonPeg®), 50, 80, 100, 120 or 150 micrograms powder for solution for injection in pre-filled pen, in combination with ribavirin (Rebetol®), 200mg capsules No. (488/08) Schering-Plough UK and Ireland

04 July 2008

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

pegylated interferon α 2b (ViraferonPeg®) in combination with ribavirin (Rebetol®) is accepted within NHS Scotland for the treatment of adult patients with chronic hepatitis C who have failed previous treatment with interferon alfa (pegylated or non-pegylated) and ribavirin combination therapy or interferon alfa (pegylated or non-pegylated) monotherapy.

A sustained virologic response rate of 23% was achieved in a single arm study where relapsed or non-responding patients were treated with peginterferon α 2b and ribavirin.

Re-treatment was more cost-effective with patients who had previously responded but relapsed compared to patients who did not respond to initial therapy.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

The combination of peginterferon α 2b and ribavirin is indicated in adult patients with chronic hepatitis C who have failed previous treatment with interferon alfa (pegylated or nonpegylated) and ribavirin combination therapy or interferon alfa (pegylated or nonpegylated) monotherapy.

Dosing information

Peginterferon α 2b 1.5 micrograms/kg/week, given subcutaneously, once weekly and ribavirin from 800 to 1,400mg daily (based on weight), orally each day in two divided doses.

Product availability date

November 2007

Summary of evidence on comparative efficacy

Up to 80% of patients infected with the hepatitis C virus become chronically infected and most of these will show evidence of chronic hepatitis, which may progress to cirrhosis or hepatocellular carcinoma. There are 6 genotypes of the hepatitis C virus and response to treatment varies between them. Peginterferon α 2b is a long acting immunomodulator, the actions of which include inhibition of viral replication in virus-infected cells. Ribavirin is an antiviral that has no effect on eliminating hepatitis C in clinical trials but which enhances the effects of peginterferons.

Evidence came from an unplanned interim analysis of a single arm multicentre study of 1354 adult patients with chronic hepatitis C, regardless of genotype, with moderate to severe hepatic fibrosis who had failed to respond to, or relapsed after, previous therapy with interferon α (pegylated or non-pegylated) plus ribavirin. The main objective was to estimate sustained virologic response (SVR) after treatment with peginterferon α 2b 1.5 microgram/kg/week and ribavirin 800 to 1,400mg/day for 48 weeks. SVR was defined as undetectable plasma hepatitis C virus, ribonucleic acid (HCV) RNA at the end of 24 weeks of post treatment follow-up and the rate of achievement of this was the primary efficacy endpoint. The hypothesis was that the SVR rate in non-responders and relapse patients is greater than 10%. Patients who were HCV RNA positive at week 12 could be enrolled in a maintenance dose study at week 18.

The rate of SVR achieved was 23% (303/1336; 99% confidence intervals (CI): 20% to 26%), giving a lower 99% CI margin above the hypothesised value. Multivariate analysis showed that the SVR rate was lower in those who previously received combination therapy with peginterferon (16%) versus 25% who previously received interferon. Previous non-responders had a lower SVR rate than those who had relapsed. Genotype and fibrosis score were also predictors of SVR.

Undetectable HCV RNA at treatment week 12 was an important indicator of SVR in this study. Of the 37% of patients with undetectable plasma HCV RNA levels at treatment week 12, 57% (282/499) achieved SVR. Patients with detectable HCV RNA at treatment week 12 were unlikely to achieve SVR. As well as fibrosis scores, for those with undetectable HCV viral load at treatment week 12, genotype was a predictor of SVR, with genotype 1 having an SVR of 48%, genotype 2 achieving 74%, genotype 3 72% and genotype 4 achieving an SVR of 60%.

Summary of evidence on comparative safety

All 1341 subjects in the Safety Population received treatment in this trial. Because of the study design, the percentage of subjects receiving treatment decreased from 93% (1243/1341) at treatment week 18 to 50% (669/1341) at treatment week 24. Forty-five % of subjects (598/1341) received 48 weeks of treatment.

Overall the pattern of adverse events (AEs) was qualitatively as expected (compared to a treatment naïve group) and there were no new safety issues.

Nearly all the subjects (97%) experienced at least one treatment-emergent AE. The incidence of serious adverse events (SAEs) was similar to the incidence reported in treatment naïve patients. Severe AEs were reported in 22% of subjects. Thrombocytopenia (2%) and neutropenia (7%) were overall more commonly seen in this population compared with treatment naïve.

In this analysis, 82 subjects received a new maximum dose of 1400mg of ribavirin. There was no meaningful difference in the rate of treatment discontinuation, overall adverse events, or serious adverse events in subjects receiving the 1400 mg dose in comparison to those receiving the 800 mg, 1000 mg, or 1200 mg doses. The only adverse event that appeared to occur at a higher rate in the 1400 mg group was vomiting (18% vs. 6%, 10%, and 8% for the 3 other groups, respectively), however none were serious adverse events.

Summary of clinical effectiveness issues

These results were based on an unplanned interim analysis in a single arm study.

Patients in this study generally experienced individual AEs with a lower frequency than treatment naïve patients in a separate study. This is likely due to a variety of factors including the exclusion of subjects with a history of moderate or severe depression and subjects with intolerance to ribavirin/interferon based on their prior treatment experience. Additionally, subjects who experienced significant AEs with prior treatment may have chosen to not be retreated. Likewise investigators may have chosen not to retreat such subjects even if the subjects were willing to be retreated.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis comparing retreatment with pegylated interferon and ribavarin to standard care (no retreatment). A lifetime model was used which allowed for an initial test of early virological response (EVR) and for treatment only to continue in patients who demonstrated such a response. Longer term events in the model included cirrhotic states, hepatocellular carcinoma and liver transplant. Patients who achieved an SVR were assumed to remain in the viral clearance state for the rest of their lives with a constant quality of life. Clinical inputs to the model were taken from the single arm multicentre study for SVR and EVR rates; longer term event rates were taken from other published health technology assessments of hepatitis C treatments. Quality of life values were taken from published sources.

The results of the model indicated that the baseline cost per QALY was £11389. Cost-effectiveness estimates for subgroups of patients were also presented. These indicated that the cost per QALY was £4205 in genotype 2-4 patients and £17676 in genotype 1 patients.

In terms of the response to previous treatment, those patients who had previously been termed as non-responders were the least cost-effective group to offer retreatment to; the cost per QALY was £17658. Sensitivity analysis indicated that the results were generally robust and the ratios remained under £20000.

The main weakness of the economic analysis related to the clinical data feeding into the model. The SVR and EVR results were derived from a study which was a non-randomised, non-placebo-controlled open label study and therefore the clinical evidence in the economic model is of a weaker form. However, the provision of sensitivity analysis on these parameters was helpful. A further weakness to note was that no allowance was made in utility values to account for side-effects of treatment.

The economic case was based on one attempt at re-treatment and not multiple attempts.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published a clinical guideline in December 2006 on the Management of Hepatitis C. However, the guideline only covers the retreatment, with pegylated interferon and ribavirin, of those who have previously received non-pegylated interferon with or without ribavirin and so does not fully cover the indication discussed in this submission.

Additional information: comparators

No other products are licensed for this specific indication, i.e. the re-treatment with peginterferon α after initial treatment with peginterferon α. Note that proprietary names are used in the cost table: this is because of licence restrictions.

Cost of relevant comparators

Drug	Dose regimen	Cost per 48 weeks (£)
Peginterferon α 2b (ViraferonPeg®)	**1.5 microgram/kg/week, subcutaneously**	**7955**
Ribavirin (Rebetol®)	**800 to 1400mg (weight based) daily, orally**	**5513**

Additional information: budget impact

The manufacturer estimated that the budget impact would be £287k in year one rising to £546k in year five, including drug and monitoring costs. The figures assumed that EVR testing would occur at week 12 and that treatment would be continued only on to 48 weeks in those patients who demonstrated a response.

1680 patients were assumed to be eligible in year one rising to 2050 patients in year five. Of these, the manufacturer assumed 33 patients would be treated in the first year rising to 59 in year five. These estimates work out overall at only 2% and 2.8% of eligible patients in years one to five respectively, although the rates within the three categories of previous treatment response did vary (it was over 5% in the 'relapser' group as they are more likely to achieve a response with retreatment and hence be offered further drug therapy).

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including ***12 May 2008.***

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted reference, shaded grey, was additional to information supplied with the submission.

European Medicines Agency (EMEA). European public assessment report (EPAR) for ViraferonPeg. www.emea.eu.int