# Scottish Medicines Consortium

## peginterferon alfa-2a, 135 microgram/mL and 180 microgram/mL pre-filled injections of solution for subcutaneous injection (Pegasys®) No. (561/09)

## Roche Products Limited

10 July 2009

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

**peginterferon alfa-2a (Pegasys®)** is accepted for use within NHS Scotland in combination with ribavirin for the treatment of chronic hepatitis C in adult patients who have failed previous treatment with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin.

Non-responders to previous hepatitis C treatment, predominantly with virus genotype 1, achieved sustained viral responses of 8% and 15% following 48 weeks and 72 weeks of combination treatment respectively.

The manufacturer did not provide comparative clinical or cost-effectiveness data versus peginterferon alfa-2b.

Overleaf is the detailed advice on this product.

**Chairman,**
**Scottish Medicines Consortium**

## Indication

Peginterferon alfa-2a is indicated in combination with ribavirin for the treatment of chronic hepatitis C in adult patients who have failed previous treatment with interferon alfa (pegylated or non-pegylated) alone or in combination therapy with ribavirin.

## Dosing information

In treatment experienced patients 180 microgram subcutaneously, once weekly for 48 weeks in combination with ribavirin 1,000mg (patients <75kg) or 1,200mg (patients ≥75kg) orally each day in two divided doses.

In patients with virus genotype 1 the recommended total duration of therapy is 72 weeks.

Patients with detectable virus at week 12 should stop therapy.

Treatment should be initiated only by a physician experienced in the treatment of patients with hepatitis C.

## Product availability date

Licence extension approved 28 November 2008

## Summary of evidence on comparative efficacy

Peginterferon alfa-2a is a chemically modified form of human recombinant interferon alfa-2a with improved pharmacokinetic properties of the active moiety resulting in a reduction of the number of weekly injections compared with standard, non-pegylated interferon.

The current submission under review by SMC is an extension to the marketing authorisation that allows retreatment in patients who have failed a previous course of hepatitis C treatment with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin.

The pivotal phase III parallel group study was conducted to compare the efficacy and safety of 48 and 72 weeks of treatment with peginterferon alfa-2a plus weight adjusted ribavirin in patients who had not responded to previous peginterferon alfa-2b (≥1.0 microgram/kg/week) plus ribavirin (≥800mg/day) for at least 12 weeks. Patients aged ≥18 years with serological evidence of hepatitis C infection (HCV RNA >600IU/mL) and hepatic biopsies consistent with chronic hepatitis C (CHC) were randomised in a 2:1:1:2 ratio to one of four treatment groups. Two groups received a high dose induction regime with peginterferon alfa-2a, 360 micrograms once weekly for 12 weeks followed by peginterferon alfa-2a 180 micrograms once weekly for 60 weeks (group A, n=317) or 36 weeks (group B, n=156) and two groups received the standard dose of 180 micrograms once weekly for 72 weeks (group C, n=156) or 48 weeks (group D, n=313). All patients received ribavirin (1,000mg/day in patients weighing <75kg or 1,200mg/day in patients weighing ≥75kg) and all treatment periods were followed by an untreated 24-week follow-up period. Patients had compensated liver disease without evidence of hepatocellular carcinoma; 91% were infected with genotype 1 and 28% had transition to cirrhosis or cirrhosis.

The primary efficacy endpoint was sustained virological response (SVR), defined as the percentage of patients with undetectable HCV RNA (<50 IU/mL) based on a single last undetectable HCV RNA measured ≥20 weeks after the end of the actual treatment period. The SVR rates in groups A and C (72 weeks) were 16% and 14% and in groups B and D (48 weeks) were 7% and 9%. Statistical hypotheses included demonstrating that SVR in group A

(high induction dose and 72 weeks of treatment) was superior to group D (standard dose and 48 weeks of treatment). SVR was significantly higher in group A (16%) than in group D (9%) (Odds Ratio 2.0; 95% Confidence Interval [CI]: 1.21 to 3.31). Pooled analysis demonstrated that SVR was significantly higher in the groups receiving 72 weeks versus 48 weeks of study treatment (16% versus 8%, Odds Ratio 2.22 [95% CI: 1.40 to 3.52]) but there was no significant difference in SVR in the high induction dose groups compared with the groups receiving standard dose (13% versus 10%, Odds Ratio 0.98 [95% CI: 0.63 to 1.51]). Between 11% and 24% of patients across all groups achieved virological suppression at week 12. In patients with and without complete viral suppression at week 12, SVR rates were 49% and 4% respectively. SVR by predictive factors, for treatment periods of 72 weeks versus 48 weeks were; genotype 1, 14% vs. 7.3%; genotypes other than 1, 33% vs. 16%; high viral load >800,000 IU/ml, 12% vs. 6.9%; low viral load ≤800,000 IU/ml, 31% vs. 13%; cirrhosis 4.8% vs. 4.5% and non-cirrhosis 20% vs. 9.3%.

A 48-week open-label re-treatment study in 64 CHC patients was also conducted. Patients had previously been treated for 24 weeks with peginterferon alfa-2a (180 micrograms) plus ribavirin (800 or 1,000/1,200mg) and were required to have documented virological end-of-treatment response followed by a relapse at the end of the 24-week follow-up period (ie week 48). It was recommended that patients received the same dose of interferon as they had received at the end of the previous study; 60 patients received 180 micrograms once weekly and 4 patients received 135 micrograms once weekly. The ribavirin dosage was weight-based and given twice daily: 52 patients received ≥1,000mg daily and 12 patients received ≤800mg daily. The primary efficacy endpoint was SVR, defined as a single undetectable serum HCV-RNA measurement at week 72. A total of 35 patients (55%) achieved an SVR. A total of 51% (n=23/45) of patients with genotype 1 and 64% (n=9/14) of patients with genotype 2 or 3 achieved an SVR.

## Summary of evidence on comparative safety

In the pivotal study, nearly all patients (≥96% in all treatment groups) reported at least one adverse event (AE). Of the total safety population, 50% received combination therapy for 72 weeks. The frequency of severe AEs was higher in the two groups receiving 72 weeks of treatment (24% in groups A and C) than in the two groups receiving 48 weeks of treatment (16% in group B and 20% in group D). Overall, a total of nine patients among the four treatment groups experienced life-threatening AEs. Between 4% and 5% of patients in groups A, C, and D and 1% of patients in group B experienced serious AEs considered related to study treatment.

The most common types of serious AEs reported were infections, blood and lymphatic disorders and gastrointestinal disorders. There were five deaths; two patients were assigned to 72 weeks of treatment, all were considered unrelated to study treatment. No apparent differences in the frequency or types of treatment-related serious AEs were observed among the four treatment groups.

Premature treatment withdrawals were higher in the groups receiving 72 weeks of treatment (peginterferon alfa-2a 12%, ribavirin 11%) than in the groups receiving 48 weeks of treatment (peginterferon alfa-2a 5.8%, ribavirin 6.6%). Dose modification occurred in a comparable proportion of patients across the four treatment groups. Neutropenia was the main reason for discontinuation with peginterferon alfa-2a (12% to 16%) and anaemia was the main reason for discontinuation with ribavirin (15% to 21%).

Overall the most frequently reported types of adverse events were those already known to associate with peginterferon and ribavirin therapy; results from three 72-week studies in

treatment naïve patients were similar to the pivotal study and no new safety concerns were identified.

## Summary of clinical effectiveness issues

There are no comparator studies of peginterferon alfa-2a versus peginterferon alfa-2b, which is also licensed for patients who have failed previous hepatitis C treatment. SMC experts are in agreement that the frequency of retreatment is very low where patients have had pegylated interferon as a first course of treatment.

In the pivotal study, induction with high-dose peginterferon alfa-2a did not improve treatment outcome. However, prolonging therapy from 48 to 72 weeks resulted in an increased SVR from about 8% to about 15% in a study population that included patients with characteristics that are less likely to achieve an SVR; genotype 1 (91% of patients in study), cirrhosis (27%), high baseline HCV RNA viral load (78%), higher body weight (mean weight = 81kg), black race (8.6%) and non-responders to prior treatment with acceptable dose and duration (100%). In practice, although this means an increase in cure of the viral disease, the European Medicines Agency (EMEA) notes that there is still a remaining risk for complications from cirrhosis.

As most patients (91%) were infected with HCV genotype 1, the additional benefit of increasing treatment duration from 48 to 72 weeks in patients with genotypes other than 1 is unclear.

In a multiple logistic regression analysis of the pivotal study, complete virus suppression at week 12 was shown to be the strongest predictor of SVR, irrespective of whether baseline prognostic factors were favourable or unfavourable. This provides a treatment stopping rule which is reflected in the Summary of Product Characteristics.

Extension of treatment to 72 weeks increased the number of adverse events with prevalent and sustained tolerability problems, however overall the most frequently reported types of adverse events were those already known to be associated with peginterferon alfa-2a and ribavirin therapy. A study will be conducted to provide further assurance of the safety of the extended treatment duration.

In the supporting study with relapsed patients, patients with genotype 1 may have received suboptimal treatment in terms of treatment duration and ribavirin dose in the initial study since 24 weeks of treatment with peginterferon alfa-2a and 800mg ribavirin is not the standard of care for patients with genotype 1 infection. The EPAR notes that conceptually there is support for the notion to retreat relapsed patients. However due to limitations in the available data the optimal treatment duration for this patient group has not been determined.

Peginterferon alfa-2a is available as a pre-filled syringe. The content of one pre-filled syringe is administered as one dose. Peginterferon alfa-2b is available as a pre-filled pen and the dose is adjusted according to the patient's weight. Patients may find peginterferon alfa-2a easier to administer.

In patients infected with genotype 1, not responding to prior treatment with peginterferon and ribavirin combination therapy, peginterferon alfa-2a is licensed for 72 weeks. However, a retreatment duration greater than 48 weeks has not been studied with peginterferon alfa-2b and ribavirin combination therapy.

## Summary of comparative health economic evidence

The manufacturer provided a cost-utility analysis comparing retreatment with peginterferon alfa-2a in combination with ribavarin to 'no treatment' in patients who have failed previous treatment with pegylated interferon alone or in combination with ribavarin. In terms of the choice of comparator, it should be noted that there is an alternative pegylated interferon product with a licence for retreatment which was accepted for use by SMC last year but experts suggest that it is reasonable to assume that the predominant strategy is 'no treatment'. A Markov model with a lifetime horizon was used, which seemed appropriate for a chronic disease and allowed for health states such as cirrhosis, hepatocellular carcinoma and liver transplantation. The model considered three subgroups of patients given different durations of therapy and response rates to treatment: genotype 1 patients who did not respond to previous treatment; patients with genotype other than 1 who did not respond to previous treatment and; patients of all genotypes who relapsed following previous treatment.

Early virological response (EVR) and sustained virological response (SVR) rates were key drivers of the model, with the EVR determining whether or not treatment was continued after 12 weeks. EVR and SVR rates for the treatment arm were taken from the clinical trials and it was assumed that patients in the no treatment arm had zero rates of SVR. Patients achieving an SVR were assumed to be cured of the condition, an assumption common to other hepatitis C models. Transition probabilities for the other states were taken from the literature. Utility values were taken from published sources.

The results indicated a cost per QALY of £2,898 per QALY gained (based on additional costs of £1,902 and 0.66 extra QALYs) in genotype 1 non-responders. For non-responders with genotype other than 1 - the figure was £619 per QALY gained (based on additional costs of £656 and 1.06 QALYs), and peginterferon alfa-2a combination retreatment was dominant for the relapser subgroup. In all cases, much of the additional drug acquisition costs associated with retreatment (around £5k to £6k) were offset by lower costs from not progressing to other (expensive) health states in the remainder of the model.

Extensive sensitivity analysis was provided. While the results were relatively stable the analysis showed that the results were most sensitive to changes in the SVR rate or the time horizon. A cost per QALY of £30,000 was reached if the SVR fell to 3% in the case of the first two subgroups or 5% in the case of the third subgroup (a fairly substantial fall in the case of this latter group). A time horizon of 5 years resulted in cost-effectiveness ratios of £36,873, £25,240 and £11,448 in each subgroup respectively.

Whilst there were some limitations in the clinical data used for the non-responders with genotype other than 1 and relapsed patients, the analysis was generally well-conducted, used similar model structures and data sources as other submissions considered by SMC and indicated that treatment is relatively cost-effective compared to no retreatment. The clinical effectiveness and cost-effectiveness relative to peginterferon alfa-2b were not assessed.

## Summary of patient and public involvement

A Patient Interest Group Submission was not made.

## Additional information: guidelines and protocols

Scottish Intercollegiate Guidelines Network (SIGN); Guideline No. 92. Management of Hepatitis C, published December 2006. SIGN states that patients with CHC who have had unsuccessful treatment with non-pegylated interferon and ribavirin should be considered for pegylated interferon and ribavirin retreatment. Treatment recommendations for patients who have failed prior therapy with pegylated interferons and ribavirin are not stated. This guideline predates the extended licensed indication of peginterferon alfa-2a that is under review in this submission.

National Institute for Health and Clinical Excellence (NICE): the expected date of issue of a multiple technology appraisal on peginterferon alfa and ribavirin for the treatment of chronic hepatitis C is October 2010. This is a part review of Technology Appraisal (TA) 75 and TA 106.

## Additional information: comparators

Pegylated interferon alfa-2b (ViraferonPeg®) in combination with ribavirin (Rebetol®) is licensed for the retreatment of Hepatitis C where previous therapy has failed.

## Cost of relevant comparators

| Drug | Dose regimen | Cost per 48 weeks (£) | Cost per 72 weeks (£) |
|---|---|---|---|
| **Peginterferon alfa-2a (Pegasys®)** | **180 microgram once weekly subcutaneously** | **6,092** | **9,138** |
| **Ribavirin (Copegus®)** | **1,000 to 1,200mg (weight based) daily orally** | **4,039** | **6,059** |
| | **Total for combination** | **10,131** | **15,197** |
| Peginterferon alfa-2b (Viraferon Peg®) | 1.5 microgram/kg/week, subcutaneously | 6,504 | N/A |
| Ribavirin (Rebetol®) | 800 to 1,400mg (weight based) daily orally | 3,276 | N/A |
| | Total for combination | 9,780 | N/A |

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 28 April 2009. Calculated costs are based on a 70kg patient. Proprietary names are used in the cost table due to licence restrictions. For Pegasys® the recommended total duration of therapy is 48 weeks for genotype non-1 patients and 72 weeks for genotype 1 patients. Copegus® is indicated for use with Pegasys® but currently not for this extended indication under review. Doses for ViraferonPeg® and Rebetol® are calculated using a dose calculator in the ViraferonPeg® SPC for a weight range 65-75kg. The summary of product characteristics for ViraferonPeg® states that all patients, irrespective of genotype, should receive 48 weeks of therapy; longer re-treatment durations in genotype 1 patients have not been studied. Rebetol® is indicated for use with ViraferonPeg® in this extended indication. N/A not applicable.

## Additional information: budget impact

The manufacturer estimated a gross budget impact of £288k in year one rising to £908k in year five. This estimate included drug acquisition costs and drug monitoring/surveillance costs (approximately 90% is drug cost). No net budget impact was presented as it was assumed that no patients are currently being offered re-treatment with peginterferon alfa. These figures also assumed that EVR testing occurs at week 12 and only patients who show a response continue with the recommended duration of therapy.

Forty-two patients were assumed to be treated in year one: 20 genotype -1 non-responder patients; 2 non-responder patients with genotype other than 1; and 20 relapser patients. This rose to 173 in year five (89 genotype-1 non-responder patients, 10 non-responder patients with genotype other than 1 and 75 relapsed patients). The numbers offered treatment represented about 2-3% of the eligible patient population in the case of non-responder patients and 4-5% of eligible patients in the case of relapsers. Higher numbers of relapsed patients were assumed to be given retreatment given the higher chances of a treatment success in this group. All retreatment was assumed to be with peginterferon alfa-2a i.e. there would be no use of peginterferon alfa-2b in this extended indication.

***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 13 June 2009.*

*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 references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.*

Jensen DM, Marcellin P. Rationale and design of the REPEAT study: a phase III, randomized, clinical trial of peginterferon alfa-2a (40kDa) plus ribavirin in non-responders to peginterferon alfa-2b (12kDa) plus ribavirin. European Journal of Gastroenterology and Hepatology 2005; 17;899-904

Jensen DM, Marcellin P, Freilich B, Andreone P, Di Bisceglie A, et al. Re-treatment of patients with chronic hepatitis C who do not respond to peginterferon alfa-2b. Annals of Internal Medicine 2009;150;528-540.

The European Medicines Agency (EMEA) European Public Assessment Report. Peginterferon alfa-2a (Pegasys®). 19/12/2008, EMEA H-C-395. www.emea.europa.eu