Scottish Medicines Consortium

pegylated Interferon alfa 2a, 180 mcg for subcutaneous injection (Pegasys®) No. (186/05)

Roche

New indication (chronic hepatitis B)

10 June 2005

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 alfa 2a (Pegasys®) is accepted for use within NHS Scotland for the treatment of HBeAg-positive or HBeAg-negative chronic hepatitis B in adult patients with compensated liver disease and evidence of viral replication, increased ALT and histologically verified liver inflammation and/or fibrosis.

Compared with conventional interferon alfa 2a, it offers comparable efficacy and the convenience of once-weekly rather than three-times weekly subcutaneous administration. It has been shown to be cost-effective when compared to a number of comparator medicines in a range of patient groups.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Pegylated Interferon alfa 2a, 180 mcg subcutaneous (Pegasys®)

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Licensed indication under review

Treatment of HBeAg-positive or HBeAg-negative chronic hepatitis B in adult patients with compensated liver disease and evidence of viral replication, increased ALT and histologically verified liver inflammation and/or fibrosis.

Dosing information under review

180 micrograms once weekly for 48 weeks by sub-cutaneous administration in the abdomen or thigh.

UK launch date

March 2005

Comparator medications

Conventional interferon alfa 2a and alfa 2b. Lamivudine. Adefovir dipivoxil.

Cost per treatment period and relevant comparators

Annual* Basic NHS Costs (C osts are not comparable due to variation in duration of therapy)

Pegylated interferon alfa 2a 180 mcg once weekly	**£6867***
Interferon alfa 2a 5-10MIU (Roferon A) subcutaneously 3 x weekly	£4699-£8224**
Interferon alfa 2b (Viraferon) 5-10 MIU subcutaneously 3 x weekly	£4701-£9402
Interferon alfa 2b (Intron A) 5-10 MIU subcutaneously 3 x weekly	£3370-£6739
Adefovir dipivoxil 10mg daily	£3832
Lamivudine 100mg daily	£1018***

* The optimum duration of treatment of chronic hepatitis B is currently unknown and, for each treatment option, depends on clinical factors like HBeAg seroconversion. Pegylated interferon alfa 2a is licensed for a fixed period of 48 weeks and the suggested duration for other interferons is 4-6 months.

** The optimal schedule has not been established but the usual dose of Roferon A is 2.5-5 MIU/m^2 The dose above is based on 2m^2 but below this the annual cost of Roferon A can reduce to £3526 -£7050 per annum at a dose of 4.5 to 9 MIU 3 x weekly.

*** Oral therapy may last for approximately 5 years.

Summary of evidence on comparative efficacy

Interferon alfa 2a is an immunomodulating agent associated with a reduction of disease activity in hepatitis B. Pegylation increases the persistence of the interferon in the blood allowing less frequent dosing.

Pegylated interferon alfa 2a monotherapy 180 mcg once weekly has been compared to lamivudine monotherapy 100 mg daily and a combination of lamivudine and pegylated interferon alfa 2a in two phase III studies, one of which recruited patients positive for hepatitis B 'e' antigen (HBeAg) while the other recruited HBeAg-negative patients. Pegylated interferon alfa 2a monotherapy has also been compared to conventional interferon alfa 2a in a phase II dose-finding trial in HBeAg-positive patients.

All of the above trials recruited patients with serological, biochemical and histological evidence of chronic hepatitis B and excluded patients with decompensated liver disease, non-viral chronic liver disease as well as other serious diseases and their therapy.

Primary endpoints

Table: Response rates for primary end points in Phase III trials at end of follow-up

End-point	**HBeAg seroconversion**	**HBV DNA suppression <100 000 cp/ml**	**HBV DNA suppression <20 000 cp/ml**	**ALT Normalisation**
Patient category	*BeAg positive*	*HBeAg positive*	*HBeAg negative*	*HBeAg negative*
Peg IFN alfa 2a monotherapy	87/271 (32%)	87/271 (32%)	76/177 (43%)	105/177 (59%)
			95% CI 36%, 51%	95% CI 52%, 67%
Peg IFN alfa 2a + lamivudine	73/271 (27%)	92/271 (34%)	79/179 (44%)	107/179 (60%)
			95% CI 37%, 52%	95% CI 52%, 67%
Lamivudine monotherapy	52/272 (19%)	60/272 (22%)	53/181 (29%)	80/181 (44%)
			95% CI 23%, 36%	95% CI 37%, 52%
p values				
Peg IFN alfa 2a monotherapy vs lamivudine monotherapy	<0.001	=0.012	=0.007	=0.004
Combination therapy vs lamivudine	=0.023	=0.003	=0.003	=0.003
Combination therapy vs Peg IFN alfa 2a	=0.23	=0.65	N/A	N/A

HBeAg: Hepatitis B e antigen **HBV DNA**: hepatitis B viral DNA **ALT**: alanine aminotransferase **CI**: confidence intervals **Peg IFN alfa 2a**: pegylated interferon alfa 2a 180 mcg/week. **Lamivudine dose** 100mg daily

In the Phase III trial which recruited 814 HBeAg-positive patients, pegylated interferon alfa-2a monotherapy achieved a significantly higher rate of HBeAg seroconversion after 48 weeks' treatment and 24 weeks' follow-up compared to lamivudine (32% vs 19%, p<0.001). The combination of lamivudine and pegylated interferon alfa-2a was associated with a 27% rate of seroconversion which did not represent a significant improvement over pegylated interferon alfa 2a alone, but was significantly superior to lamivudine monotherapy (p=0.23 and p=0.023 respectively).

Similarly, significantly more patients treated with pegylated interferon alfa-2a as monotherapy or in combination with lamivudine achieved a reduction in hepatitis B viral DNA levels (HBV DNA) to below 100,000 copies/ml compared to lamivudine alone (32% and 34% versus 22%, p=0.012 and p=0.003 respectively). Again, the combination of pegylated interferon alfa-2a and lamivudine was not statistically different to pegylated interferon alfa-2a alone (p=0.65).

In the phase III trial involving 537 HBeAg-negative patients, the primary end-points were normalisation of alanine aminotransferase (ALT) with the upper limit of normal (ULN) defined as 30 IU/L, and suppression of HBV DNA to <20,000 copies/ml with both being assessed after 48 weeks treatment and 24 weeks follow-up. ALT normalisation was achieved by 59% of patients on pegylated interferon alfa 2a monotherapy, 60% of patients in the combination therapy group and 44% with lamivudine monotherapy. The differences were significant for comparisons between pegylated interferon and lamivudine but not between pegylated interferon alfa 2a monotherapy and combination therapy. There was a similar pattern for suppression of HBV DNA with response rates of 43%, 44% and 29% respectively.

Secondary endpoints, sub-group analysis and uncontrolled trials

In the Phase III trial which recruited HBeAg-positive patients, HbsAg seroconversion was achieved by 3% of patients in each of the pegylated interferon alfa 2a groups (monotherapy and combination) and by no patients in the lamivudine group. In HBeAg negative patients, the response rates were 2-3% and zero respectively. In this trial at end of treatment, lamivudine resistant YMDD mutations were detected in significantly more patients who had received lamivudine monotherapy than those who had received combination therapy 32/179 (18%) vs 1/173 (<1%, p<0.001). Histological response rates were similar between the three groups.

In the Phase II trial, with treatment for 24 weeks and a further 24 weeks' follow-up, no end point was identified as primary, but there were no significant differences in response rates between pegylated interferon alfa 2a (with data pooled for three doses) and conventional interferon alfa 2a for HBeAg loss, HBeAg seroconversion, suppression of HBV DNA to <500,000 copies/ml or normalisation of ALT. For a combined response, including all three of HBeAg loss, viral DNA suppression and normalisation of ALT levels, there was a significantly higher response rate for pegylated interferon alfa 2a pooled than for conventional interferon alfa 2a (24% vs 12%, p=0.036).

The submission provided un-referenced data on quality of life assessment using the short-form 36 instrument. During treatment, pegylated interferon alfa 2a plus lamivudine was associated with lower quality of life than lamivudine alone. The differences were stated to be modest and may reflect side effects.

Summary of evidence on comparative safety

The rate of occurrence of adverse events was similar between pegylated interferon alfa 2a groups (monotherapy and in combination with lamivudine), but greater than in the lamivudine monotherapy groups, whether for overall incidence or for individual adverse events. For example, in HBeAg negative patients the proportion of patients with at least one adverse event was 155/177 (88%) with pegylated interferon alfa 2a monotherapy, 155/179 (87%) with combination therapy and 86/181 (48%) with lamivudine alone. The overall rate of serious adverse events was similar across all three treatment arms, e.g. 5%, 7% and 3% respectively in HBeAg-negative patients.

The overall adverse event profile for pegylated interferon alfa 2a in CHB was similar to that observed previously in hepatitis C (pyrexia, fatigue, headache, myalgia, alopecia, arthralgia etc). However, the Summary of Product Characteristics for pegylated interferon alfa 2a provides evidence that the incidence of undesirable effects at a dose of 180 micrograms weekly over 48-weeks was lower in patients being treated for hepatitis B than for those treated for hepatitis C.

Summary of clinical effectiveness issues

Comparison with conventional interferon alfa 2a therapy is limited to a dose-finding Phase II trial in which there was no significant difference between the pegylated and conventional forms of interferon alfa 2a apart from response rates for a combined end-point. The pegylated formulation is administered once-weekly for a finite period (48 weeks) as opposed to three times weekly for the conventional injection with a suggested duration of 4-6 months.

Lamivudine is given once daily by mouth with no limitation on duration of therapy. Resistance tends to develop with prolonged use, although response rates e.g. for HBeAg seroconversion, may continue to increase with continued treatment. Pegylated interferon alfa 2a was associated with significantly better viral, serological and biochemical response rates than lamivudine in both HBeAg-positive and -negative patients, with no significant difference between pegylated interferon alfa 2a as monotherapy and in combination with lamivudine.

There are no specific data on other patient sub-groups such as treatment naïve patients or those with lamivudine-resistant infections. Pegylated interferon alfa 2a is indicated only in patients with compensated liver disease, and those with decompensated disease were excluded from all trials.

The Phase II trial was based on centres in Australasia, and the proportion of Asian patients exceeded 97%. The two phase III studies recruited more widely, but the proportion of Asian patients remained high (about 60% of HBeAg-negative patients and 86% of HBeAg-positive).

Treatment duration corresponded to the licensed treatment period in both Phase III trials, with results reported after a further 24 weeks of follow-up. No further data are available on durability of response.

Summary of comparative health economic evidence

A lifetime state transition Markov model was provided as part of the submission. This compared the cost-effectiveness of pegylated interferon alfa 2a over 48 weeks against a range of comparators; conventional interferon alfa 2a (for 24 weeks), lamivudine (for 48 weeks or four years) and no treatment. Cost effectiveness ratios were presented separately for HBeAG negative and HBeAg positive patients. For HBeAg positive patients the incremental cost effectiveness ratio (ICER) for pegylated interferon alfa 2a versus the conventional formulation was £14,000 per QALY, £5300 per QALY versus 48 weeks of lamivudine, £6000 per QALY versus four years of lamivudine and £2800 per QALY versus no treatment. In HBeAg negative patients the incremental cost per QALY was £3200 versus 48 weeks of lamivudine, £1900 versus four years of lamivudine and £1500 versus no treatment. One way and probabilistic sensitivity analysis indicated that even with varying the conditions the ICERs are likely to remain under £22000 per QALY.

The analysis used a range of different comparators to cover different clinical practices but market use data suggested that lamivudine is the most commonly used treatment. Lamivudine is generally given for longer than 48 weeks and therefore the most relevant comparisons presented relate to lamivudine used over a four-year time span rather than the 48 weeks of the clinical trial. The model did not take into account the effects of lamivudine resistance the inclusion of which would have improved clinical effectiveness of pegylated interferon alpha 2a.

Budget impact

The manufacturer provided budget impact estimates for years one to five of approximately £282000, £696000, £1240000, £1920000 and £2190000 respectively. The calculations assumed 212 new patients in 2005 and 261, 311, 361 and 411 new patients in each of the years thereafter. These figures assumed that pegylated interferon alfa 2a would displace the use of lamivudine, with market share of new patients on pegylated interferon alfa 2a increasing to 100% in years four and five. The figures however only include the costs of one year of lamivudine use rather than lamivudine being used on an ongoing basis, the inclusion of which would reduce the net budget impact figures above. It may be more likely that pegylated interferon alfa 2a will replace conventional interferon, lowering the budget impact considerably.

Guidelines and protocols

The Scottish Medicines Consortium (SMC) recommended pegylated interferon alfa 2a (as Pegasys®) for restricted use in adults for chronic hepatitis C in September 2002, and in May 2002 advised that pegylated interferon alfa 2b (as ViraferonPeg®) was an appropriate treatment for the same condition.

In April 2005, following a resubmission, SMC advised that adefovir dipivoxil (Hepsera) is accepted for restricted use within NHS Scotland for the treatment of chronic hepatitis B in adults with either compensated liver disease with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active liver inflammation and fibrosis, or decompensated liver disease. Its use is restricted to patients who demonstrate lamivudine resistance.

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 May 2005.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The reference numbers in this document refer to the under-noted references. Those shaded grey are additional to those supplied with the submission.

British National Formulary March 2005

Monthly Index of Medical Specialities, April 2005

Information Services Division, NHS Scotland, costs for prescription pricing

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