Scottish Medicines Consortium

Interferon beta-1b 250microgram/ml for solution for injection (Betaferon®) No. (345/07)

Schering Health Care Ltd

12 January 2007

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

ADVICE: following a full submission

interferon beta-1b (Betaferon®) is not recommended for use within NHS Scotland for the treatment of patients with a single demyelinating event with an active inflammatory process, severe enough to warrant treatment with intravenous corticosteroids, where alternative diagnoses are excluded and who are determined to be at high risk of developing clinically definite multiple sclerosis.

Although interferon beta-1b has been found to increase the time to clinically definite multiple sclerosis over 2 years, the long-term effect on the disease process remains unknown. The economic case has not been demonstrated.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Treatment of patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded and if they are determined to be at high risk of developing clinically definite multiple sclerosis.

Dosing information

250 micrograms (8 million international units) injected subcutaneously every other day. Treatment is generally started with a dose titration from 62.5 micrograms every other day.

Date of licensing or licence status on date of review

June 2006

Summary of evidence on comparative efficacy

Multiple sclerosis (MS) is a condition of the central nervous system (CNS) of unknown cause, usually diagnosed between the ages of 20 and 50 years. The disease involves areas of the CNS becoming inflamed and then damaged by the patient's own immune system resulting in scarring. Clinically isolated syndrome (CIS), involving a single white matter lesion of the CNS, is the initial clinical onset in 85% of adults who later develop MS. It has been estimated that 30-70% of patients with a CIS will go on to develop MS.

The evidence to support the use of interferon beta-1b in CIS comes from the results of the Betaferon in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT) study. This is a multi-centre, randomised, double-blind, placebo-controlled study designed to assess the efficacy, safety and tolerability of interferon beta-1b in patients with a first clinical event suggestive of MS. Eligible patients were aged 18-45 years, who had presented in the last 60 days with a first clinical event suggestive of MS of at least 24 hours duration with no other likely diagnosis. They had at least two clinically silent lesions on T2-weighted brain MRI scan of at least 3mm, one of which required to be ovoid, periventricular or infratentorial. Baseline Expanded Disability Status Scale (EDSS) score had to be 0-5.0.

Patients were randomised in a 5:3 ratio to receive interferon beta-1b (titrated up to 250 micrograms per dose, n=292) or placebo (n=176) subcutaneously every other day. Treatment was continued for up to two years or until clinically definite MS (CDMS). The study had two primary endpoints: (1) CDMS defined by slightly modified Poser criteria (relapse with clinical evidence of at least one CNS lesion (distinct from previous if initially monofocal) or sustained progression of ≥1.5 points on the EDSS score to a total of ≥2.5) and (2) time to MS as defined by McDonald criteria (using demonstration of lesion dissemination in space and time from MRI data on repeat scans). Secondary outcomes included the cumulative number of newly active lesions and the absolute change in T2 lesion volume between screening and end of study scans.

In the interferon beta-1b group, 75/292 (26%) patients had reached CDMS and 191/292 (65%) McDonald MS at the end of the study. This compared to 77/176 (44%) and 142/176 (81%) respectively in the placebo group. Based on Kaplan-Meier estimates, the two-year cumulative probability of developing CDMS was reduced from 45% in the placebo group to 28% in the interferon beta-1b group, an absolute risk reduction of 17% and a proportional hazards regression ratio (with the complete set of covariates) of 0.50 (95%CI: 0.36, 0.70), p<0.0001**,** equating to a number needed to treat (NNT) of 5.9 to prevent one case of CDMS over two years. The two-year cumulative probability of developing McDonald MS was reduced from 85% in the placebo group to 69% in the interferon beta-1b group; an absolute risk reduction of 16% and a proportional hazards regression ratio (with the complete set of covariates) of 0.54 (95%CI: 0.43, 0.67), p<0.00001**,** equating to a NNT of 6.3 to prevent one case of McDonald MS over 2 years.

Analysis of predefined subgroups (monofocal/multifocal disease, presence/absence of gadolinium (Gd) enhancing lesions and <9/≥9 T2 lesions) found a significant treatment effect in each. In the total group the treatment effects were largest with monofocal disease and less inflammatory lesions. Interferon beta-1b was also associated with a significantly lower cumulative number of new lesions and cumulative Gd enhancing lesion volume compared to placebo.

During the study there were no significant differences between active treatment and placebo in terms of patient-reported physical health or health-related quality of life measures. There was little change from baseline for these parameters.

Summary of evidence on comparative safety

No new issues were identified during the assessment of interferon beta-1b for this new indication. The most commonly reported adverse events were injection site reactions and flu-like syndrome. These were minimised during the study by allowing the use of paracetamol/ibuprofen and by use of autoinjectors. Increased liver enzymes were more frequently reported in the interferon beta-1b arm and five patients discontinued treatment for this reason.

During the BENEFIT study, neutralising antibody activity was detected at least once in 75/251 (30%) evaluable interferon beta-1b patients with 17 (23%) of these patients subsequently converting to negative status. This did not appear to be associated with a reduction in efficacy (as measured by time to CDMS) during the study period.

Summary of clinical effectiveness issues

The BENEFIT study was designed to show effect on time to CDMS and not on the long-term evolution of the disease. Therefore the long-term effects on relapse rates, progression and disability remain to be seen. The controlled phase of the study was extended to open label active treatment for all patients for up to 5 years and preliminary results are awaited.

It has been estimated that 30-70% of patients with a CIS will develop MS and so for many patients the occurrence of a CIS is of no long-term clinical consequence. Furthermore, a substantial number of patients who do develop MS have a relatively benign course of disease with little or no disability for the next 10-14 years. In the BENEFIT study, after 2 years of treatment with placebo, 56% of patients had not developed CDMS and 19% had not developed MS according to McDonald criteria.

This makes it difficult to determine how much benefit is to be gained by treating patients early after a CIS instead of waiting until a second clinical event at which time MS would be confirmed. The possible benefits of early treatment need to be balanced against the adverse drug events as well as the potential to develop neutralising activity which may reduce drug efficacy at a later stage of the disease.

Summary of comparative health economic evidence

The manufacturer submitted a lifetime Markov model to demonstrate the cost effectiveness of treating individuals with CIS using interferon beta-1b compared to no treatment. The model had six states based on EDSS scores, being CIS (EDSS 0), mild (EDSS 1 to 4), moderate (EDSS 4.5 to 6), and severe states (EDSS =6.5) and death. Costs and utilities were associated with each state.

Patients with CIS either continued in CIS, converted to mild MS at the rate observed in the BENEFIT trial or died. Patients who converted to mild MS were initially offered treatment, unless they had discontinued with the drug in the trial. Mild and moderate MS patients progressed to moderate and severe MS respectively at rates derived from Swedish registry data or died; whilst severe MS patients either died or remained at severe MS.

The results reported a cost/QALY of £32,000 for all patients with CIS, falling to £24,000 if only those with monofocal CIS are treated. Sensitivity analyses indicated the result was very sensitive to the diagnostic criteria used; adopting McDonald criteria raised the cost per QALY to £57,000.

These incremental cost-effectiveness ratios adopt an NHS/personal social services perspective and thus cannot be compared to conventional cost effectiveness criteria. The manufacturer has supplied a sensitivity analysis based on an NHS-only perspective. This reported an incremental cost/QALY of £30,000.

The comparator, costs, utilities and model structure were adequate. The main concerns are:

1. The assumption that 95% of patients with CIS convert to MS. The manufacturer was asked to reference this assumption but has explained it is an output of the model and thus not explicitly evidence based. The trial data and data from other published references suggest lower conversion rates. The modelled disease progression rates also assumed that patients in the mild disease state who receive a disease modifying drug progress to a severe disease state slightly quicker than patients who do not have therapy. This assumption, which is counter-intuitive, potentially biases the results because more people in the placebo arm receive therapy on diagnosis (having a lower discontinuation rate in the trial (10% vs 15%), incur the cost of £7,240 but receive no clinical benefit in terms of progression rates. The source of the data for the active arm was a Swedish registry study.

2. Use of a constant annual transition rate from time to definite diagnosis, although clinical data for first two years show the rate of change in year 2 is lower than in year 1. Data used in the model for the progression rate in placebo arm were higher than observed in the trial.

3. Absence of the additional costs to identify and manage this currently untreated group during the pre-diagnosis stage. Such costs could be material, requiring more MRI scans, other tests and neurologist clinics. The manufacturer provided a revised cost per QALY of £32340 assuming one additional MRI scan was needed. However, the

additional resources required to identify and manage such patients in the pre-diagnosis stage are likely to be greater than one additional scan.

In light of the reported cost/QALY for the base case, the supporting sensitivity analyses, particularly on the use of the McDonald criteria , and the concerns highlighted, the economic case for using Interferon beta-1b in CIS patients or the subgroup with monofocal CIS is not demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The National Institute for Health and Clinical Excellence (NICE) has produced a National Clinical Guideline on Multiple Sclerosis, Management and diagnosis in primary and secondary care. (February 2004). This supports use of the McDonald criteria for diagnosis of MS.

There are no guidelines or protocols specifically relating to CIS.

Additional information: previous SMC advice

In November 2003, following an abbreviated submission, SMC accepted interferon beta-1a (Avonex®) for restricted use within NHS Scotland. Avonex® is a liquid formulation which replaces a powder formulation of the same strength that requires reconstitution. It is supplied at the same price. This product is used for the treatment of selected ambulatory patients with relapsing-remitting multiple sclerosis under the provision of a risk-sharing scheme between the Scottish Executive and the manufacturer.

Additional information: comparators

Following a CIS, patients may receive a course of high dose corticosteroids to alleviate symptoms and accelerate recovery. However, the only direct comparator to interferon beta-1b for reducing the likelihood of progression to MS is interferon beta-1a (Avonex®) which is also licensed for this indication but has not been submitted to SMC.

Additional information: costs

Drug	Dose	Cost per annum
Interferon beta-1b (Betaferon®)	**250 micrograms subcutaneously every other day**	**£7259**
Interferon beta-1a (Avonex®)*	30 micrograms intramuscularly once weekly	£8502

* Note interferon beta-1a has currently not been submitted to SMC for this indication.

Additional information: budget impact

The manufacturer estimated that in 2007 about 50 patients with CIS would be treated with beta interferon-1b, rising to 150 by 2011. Market share is assumed to be 100% of all patients with CIS who sees a neurologist at the time of their first event and who are judged appropriate for treatment.

The estimated costs of the drug only during the CIS stage are £0.36 million, in 2007 rising to £1.33 million in 2011. A comparison of the costs of managing those who progress to MS with and without administering Beta interferon-1b at the CIS stage shows a net cost to the service of £0.36 million in 2007, rising to £0.90 million in 2011. In addition there would be significant service changes and resources required to introduce this treatment. These costs have not been calculated.

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 December 2006.

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. Those shaded grey are additional to those supplied with the submission.

Kappos L, Polman CH, Freedman MS et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. Neurology 2006; 67: 1242-1249.

Miller D, Barkhof F, Montalban X et al. Clinically isolated syndromes suggestive of multiple sclerosis, part 1:natural history, pathogenesis, diagnosis and prognosis. Lancet Neurology 2005; 4: 281-88.

Miller D, Barkhof F, Montalban X et al. Clinically isolated syndromes suggestive of multiple sclerosis, part 2:non-conventioanl MRI, recovery processes, and management. Lancet Neurology 2005; 4: 341-48.

National Collaborating Centre for Chronic Conditions. Multiple sclerosis. National clinical guideline for the management and diagnosis in primary and secondary care. NICE clinical guideline 008. February 2004.