Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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peginterferon-beta-1a 63, 94 and 125 microgram solution for injection in pre-filled syringe (Plegridy®) SMC No. (1018/14)

Biogen Idec Ltd.

05 December 2014

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-beta-1a (Plegridy®) is accepted for use within NHS Scotland.

Indication under review: in adult patients for the treatment of relapsing remitting multiple sclerosis.

Peginterferon-beta-1a, compared with placebo, improved annualised relapse rate in adults with relapsing remitting multiple sclerosis.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

In adult patients for the treatment of relapsing remitting multiple sclerosis.

Dosing Information

125 micrograms injected subcutaneously every two weeks. It is generally recommended that patients start treatment with 63 micrograms at dose 1, increasing to 94 micrograms at dose 2, reaching the full dose of 125 micrograms by dose 3 and continuing with the full dose (125 micrograms) every 2 weeks thereafter.

Treatment should be initiated under supervision of a physician experienced in the treatment of multiple sclerosis.

Product availability date

January 2015

Summary of evidence on comparative efficacy

Peginterferon-beta-1a is the first pegylated form of beta-interferon to be licensed for the treatment of relapsing-remitting multiple sclerosis (RRMS).[1] It binds to type 1 interferon receptors, but its exact mechanism of action is unknown. Pegylation has been shown to increase the half-life, in-vivo activity, and efficacy of therapeutic proteins while reducing their immunogenicity. The biological effects of peginterferon-beta-1a may mediate include up-regulation of anti-inflammatory cytokines, down-regulation of pro-inflammatory cytokines and inhibition of T-cell migration across the blood brain barrier.[2]

A phase III double-blind study (ADVANCE) recruited 1,512 adults aged 18 to 65 years with RRMS defined by the MacDonald criteria, who had had at least two relapses in the preceding three years with at least one in the preceding 12 months and expanded disability status scale (EDSS) score of 0 to 5. They were randomised equally to subcutaneous (SC) injections of placebo, peginterferon-beta-1a 125 micrograms every 2 weeks or every 4 weeks. At 48 weeks, the placebo group was re-randomised to peginterferon-beta-1a 125 micrograms every 2 weeks or every 4 weeks for the remainder of the two-year study. The primary outcome was annualised relapse rate (ARR) at week 48, where relapse was defined as new or recurrent neurological symptom not associated with fever or infection, lasting at least 24 hours and accompanied by new objective neurological findings confirmed by an independent evaluation committee. This was assessed using a negative binomial regression model adjusted for baseline EDSS score (<4 versus ≥4), baseline relapse rate and age (<40 versus ≥40 years) in the intention-to-treat population, which comprised all randomised and treated patients. Only results for the licensed dose of peginterferon-beta-1a, 125mcg every two weeks are presented below.[2,3]

At one year, the ARR was significantly lower with peginterferon-beta-1a every 2 weeks compared to placebo: 0.256 versus 0.397, with rate ratio versus placebo of 0.644 (95% confidence interval (CI): 0.500 to 0.831), p=0.0007. Within the ITT population dosed in year 2, ARR in the group that received peginterferon-beta-1a every 2 weeks throughout was 0.23 in year 1 and 0.178 in year 2. In the group that received placebo in year 1 and peginterferon-beta-1a every 2 weeks in year 2, ARR in the respective years was 0.418 and 0.30.[2,3]

The secondary outcome, confirmed disability progression (CDP) for 3 months, was defined in the study protocol as an increase of EDSS score of at least 1 point for patients with baseline score of at

least 1, or an increase of at least 1.5 points for patients with baseline score of 0, which was confirmed after 12 weeks. The proportion of patients with this at 1 year was significantly lower with peginterferon-beta-1a every 2 weeks compared to placebo: 0.068 versus 0.105, with hazard ratio (95% CI) of 0.62 (0.40 to 0.97), p=0.038.[2]

CDP for 6 months, as defined by the CHMP, required an increase in EDSS score of at least 1 point in patients with baseline EDSS score of 5.5 or less, and an increase of at least 0.5 point in patients with baseline EDSS greater than 5.5, that persisted for 6 months. The proportion of patients with this at 1 year was significantly lower with peginterferon-beta-1a every 2 weeks compared to placebo, with hazard ratio (95% CI) of 0.59 (0.36 to 0.98), p=0.0402.[2]

The adjusted mean number of new or newly enlarging T2-weighted hyperintense lesions at 1 year was significantly reduced in the group that received peginterferon-beta-1a every 2 weeks compared with placebo: 3.6 versus 10.9, respectively, with lesion mean ratio (95% CI) of 0.33 (0.27 to 0.40), p≤0.0001.[2]

There were no significant differences between peginterferon-beta-1a every two weeks and placebo for the quality of life outcomes, SF-36, EQ-5D or Multiple Sclerosis Impact Scale-29.[4]

Summary of evidence on comparative safety

The European Medicines Agency (EMA) considered that the safety profile of peginterferon-beta-1a was generally consistent with that of non-pegylated interferon-beta therapies. Adverse events commonly associated with beta-interferons include flu-like symptoms and injection-site reactions. In the ADVANCE study, these were reported more frequently with peginterferon-beta-1a than with placebo. Other adverse events of special interest associated with interferons include cardiovascular, hepatic and autoimmune disorders, seizures, depression, suicidal ideation, hypersensitivity reactions, laboratory abnormalities (haematological and liver function tests), infection and malignancies. In the ADVANCE study, there was a dose-dependent increase in alanine transaminase (ALT) and aspartate transaminase (AST) with peginterferon-beta-1a, but the majority of increases were to less than 3 times the upper limit of normal (ULN). The incidence of ALT and AST greater than 3 times ULN was slightly higher in the peginterferon-beta-1a groups compared with placebo.[2]

In the placebo-controlled phase, the overall incidence of adverse events (which included relapses reported as adverse events) was higher in the peginterferon-beta-1a every 2 weeks (94%) group than in the placebo group (83%) and the overall incidence of adverse events (which excluded relapses) was 93% and 79% in the respective groups. Adverse events reported with at least 2% greater frequency in the peginterferon-beta-1a groups than the placebo group included injection-site reactions, influenza-like illness, pyrexia and headache. The incidence of adverse events related to study treatment was also higher in the peginterferon-beta-1a group (90%) compared to placebo (53%), with the most common including injection-site reactions, influenza-like illness and headache. Adverse events leading to discontinuation of study treatment occurred in 5% of patients in each of the peginterferon-beta-1a groups and in 1% of patients in the placebo group. Serious adverse events were reported by similar numbers of patients across the groups: 11% and 15% in the peginterferon-beta-1a every 2 weeks and placebo groups, respectively. Relapse of MS was the most common serious adverse event and the incidence of serious adverse events, which excluded relapses, was 5% in each group. Other serious adverse events included pneumonia and urinary tract infection.[3]

Summary of clinical effectiveness issues

MS is a chronic progressive neurodegenerative disorder characterised by multifocal demyelination affecting the brain, optic nerves and spinal cord, resulting in a variety of central nervous system symptoms and often severe disability. The pathogenesis of MS remains unknown, although an autoimmune process may be involved. Approximately 85% of patients have the relapsing-remitting form of MS, which is associated with unpredictable acute episodes of neurological dysfunction, followed by recovery and periods of clinical stability. Current treatments include corticosteroids for acute relapses and disease modifying therapies, such beta-interferons, glatiramer, natalizumab, fingolimod, dimethyl fumarate, alemtuzumab or teriflunomide.[2] This is the first pegylated form of interferon-beta licensed for RRMS and it has a reduced dosing frequency, every 2 weeks,[1] compared with current standard interferon-beta treatments, which are administered every other day to every week.[5-8]

The primary endpoint, ARR, is the recommended endpoint for MS studies in patients with RRMS. Also the definition of relapse was in accordance with the widely accepted clinical definition.[2] A phase III study has demonstrated efficacy versus placebo in terms of relapse rate.[2,3] The EMA noted that the treatment effect on ARR was modest; however, the relative reduction of 30% was comparable to that seen with other interferons and was considered clinically relevant. Evidence of efficacy for CDP is less robust. Using the protocol-specified definition of CDP, which was over a 3 month period, efficacy was demonstrated relative to placebo. However, using a definition in line with CHMP guidelines, which was over a 6 month period, the treatment effect was smaller. Peginterferon-beta-1a also significantly reduced the number of new or newly enlarging T2 hyperintense lesions.[2,3]

The majority of patients recruited to the ADVANCE study were treatment-naive and had mild disease, (84% had a score ≤3.5 on the EDSS, which ranges from 0 to 10). In the subgroup of patients with the highest number of relapses (≥ 4) in the 3 years prior to study entry, no effect of peginterferon-beta-1a was seen for ARR or CDP. However, the number of patients was too small to draw firm conclusions on this.[2]

Peginterferon-beta-1a will be provided in an auto-injector which requires no reconstitution or assembly and no cold chain storage. In a small usability study (n=39), the majority of patients found the device easy to use. However, the study did not include any comparisons between the auto-injector and pre-filled syringe in terms of ease of use.[2]

There are no direct comparative data with other beta-interferons. Therefore, Bayesian network meta-analyses were performed, which included data from randomised studies of peginterferon-beta-1a SC (Plegridy®), interferon-beta-1a SC (Rebif®) and intramuscular (Avonex®), interferon-beta-1b SC (Betaferon® and Extavia®) and glatiramer acetate SC (Copaxone®) in adults with RRMS or relapsing multiple sclerosis (RMS). These indicate statistically significant differences for ARR and CDP at 3 months for peginterferon-beta-1a versus placebo, but not versus the other active interventions. The analyses were limited by heterogeneity in duration of disease, prior treatments (e.g. treatment-naive or experienced) and current standard treatments, as the included studies were from 1985 to the present. There was also heterogeneity in study duration, sample size and blinding, although sensitivity analyses were performed to account for these.

The EMA also noted the lack of comparative data for peginterferon-beta-1a and other beta-interferons. It considered that an indirect comparison, despite its limitations, indicated that the reduction of ARR and time to CDP with peginterferon beta-1a and the non-pegylated beta-interferons were in a comparable range. However, it was noted that as the magnitude of effect of beta-interferons is modest, any potential difference in effect size may be critical when switching patients from one

interferon product to the other.[2] The summary of product characteristics therefore notes that direct comparative data versus non-pegylated interferon beta or data on efficacy of peginterferon-beta-1a after switching from a non-pegylated interferon beta are not available. This should be taken into account if switching patients between pegylated and non-pegylated interferons is considered.[1]

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing peginterferon-beta-1a with current standard interferon-beta treatments: interferon-beta-1a SC (Rebif®), interferon-beta-1a intramuscular (Avonex®), interferon-beta-1b SC (Betaferon® and Extavia®), and glatiramer acetate SC (Copaxone®). SMC clinical experts have confirmed the comparators are appropriate.

A Markov cohort model with a 30-year time horizon was used in the analysis. This model was developed by the School of Health and Related Research (ScHARR) at Sheffield University for the National Institute for Health and Care Excellence (NICE) and has been used in previous submissions to both SMC and NICE for multiple sclerosis treatments. Patients enter the model at a baseline RRMS health state based on their EDSS level and can then move to a higher or lower EDSS health state each cycle. The model also accounts for patients progressing to secondary progressive multiple sclerosis (SPMS) where again they can progress to a higher or lower EDSS health state within SPMS each cycle. In line with other multiple sclerosis models, a stopping rule was included where patients discontinue treatment on entering SPMS or EDSS health state 7. Relapse was also included in the model.

The clinical data used in the economic analysis were based largely on the ADVANCE study and the results of the Bayesian network meta analyses (NMA) described above. Baseline characteristics were taken from a pooled analysis of the peginteferon-beta-1a and placebo arms of the ADVANCE study. Baseline annual transition probabilities within the RRMS health states were taken from the placebo arm of the ADVANCE study up to health state EDSS 5 but, for EDSS 6-9, a different data source (the London Ontario multiple sclerosis registry) was used due to the small number of observations in the more severe health states. For transitions from RRMS to SPMS and within SPMS, the London Ontario dataset was also used. Baseline relapse rates were based on the pooled baseline data from the ADVANCE study up to EDSS 5.5 and then a separate study was used to estimate relapse rates for the more severe health states. The results of the NMA were then applied to the baseline data to estimate the treatment efficacy for each of the drugs included in the model. The results of the NMA showed there were no significant differences between peginterferon-beta-1a and any of the comparators but the numerical differences from the CDP sustained for 3 months and ARR outcomes were included in the model.

Utility values were used in the model according to EDSS health state and relapse status. For RRMS health states, EQ-5D data from the placebo arm of the ADVANCE study were used for health states EDSS 0-5 and these were combined with UK multiple sclerosis survey data for EDSS 6-9. In addition to utility values associated with patients with multiple sclerosis, the model also included disutilities associated with caregivers. These values were taken from a multiple sclerosis survey and NICE technology appraisal of Alzheimer's disease where the maximum disutility for a caregiver was assumed to be 0.14. However, the inclusion of disutilities associated with caregivers in the base case analysis is not appropriate and should only be included as a sensitivity analysis.

Drug acquisition costs for peginterferon-beta-1a and comparators were included. It should be noted that in the base case analysis the costs of the comparator treatments used UK Risk Sharing Scheme prices rather than list prices. SMC guidance advises list prices should be used unless there is a patient access scheme in place. However as the list prices are either the same or higher than the

Risk Sharing Scheme prices, the company's cost estimates for the comparators can be considered conservative.

Administration costs were also included and were assumed to be the same for each treatment. Subsequent treatments were not included in the model and, while the company did not state why these were excluded, this is likely to be for pragmatic reasons. Disease management costs were based on a published study and were included according to EDSS level. Treatment monitoring cost estimates were based on the Summary of Product Characteristics for each treatment. The resource use associated with managing adverse events was estimated and then validated by a Delphi panel conducted by the company. The results of the base case analysis are presented in the table below.

Treatment	Total cost	Total QALYs	ICER for peginterferon-beta-1a (QALYs)
peginterferon-beta-1a	£101,354	7.32	-
glatiramer acetate	£93,955	6.90	£17,821
interferon-beta-1a 44 µg sc (Rebif®)	£100,089	7.01	£4,121
interferon-beta-1b 250 µg sc (Betaferon® and Extavia®)	£104,981	6.88	dominant
interferon-beta-1a 22 µg sc (Rebif®)	£107,072	6.99	dominant
Interferon-beta-1a intramuscular 30 µg (Avonex®)	£107,580	6.88	dominant

QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio; dominant: treatment both cost-saving and more effective.

Deterministic, two-way and probabilistic sensitivity analyses (PSA) were presented. In general, peginterferon-beta-1a remained a cost-effective treatment in most sensitivity analysis scenarios when compared with the standard interferon-beta treatments. The comparison with glatiramer acetate was more uncertain, resulting in ICERs above £30k per QALY in some scenarios. The PSA showed that the probability of peginterferon-beta-1a being cost-effective at £20k per QALY ranged from 49% for the comparison with glatiramer to 96% for the comparison with interferon-beta-1a (Avonex®).

The main weakness with the analysis is that the economic results are based on differences in efficacy between the treatments which are not supported by the results of the NMA (which showed there are no statistically significant differences between the treatments). An analysis excluding the non-significant differences and using the list prices has been provided and this showed that, compared to interferon-beta-1a 44 µg (Rebif®), peginterferon-beta-1a is cost-saving with estimated savings of £2,070 per year and is cost-neutral when compared with interferon-beta-1a (Avonex®). However, in comparison with the other interferon-beta treatments and glatiramer acetate, peginterferon-beta-1a is associated with an incremental cost of between £989 and £1,963 per annum. As it is likely that peginterferon-beta-1a would displace a proportion of each of the standard interferon-beta treatments, the company also provided the results of a weighted average comparison based on all the interferon-beta treatments. In this analysis, peginterferon-beta-1a was estimated to result in cost-savings of £311 per annum when compared with the weighted average of the comparator treatments.

When the non-significant differences are removed, although peginterferon-beta-1a is associated with an incremental cost versus some treatments, it is cost-saving or cost neutral versus others, and using

the weighted average comparison is also cost-saving. Therefore, the economic case has been demonstrated.

Summary of patient and public involvement

The following information reflects the views of the specific patient group.

- A submission was received from the Multiple Sclerosis Trust (MST), which is a registered charity.
- MST has received funding from several pharmaceutical companies in the past two years, including from the submitting company.
- Multiple sclerosis is a disease with relapses that are unpredictable in onset, severity, type of symptoms, and duration. Recovery is often incomplete, leading to accumulation of disability with each successive relapse. Residual disability may be apparent, such as impaired mobility, but may also be less overt, such as depression, fatigue, cognitive problems or sexual dysfunction. Relapses can have a significant impact on a patient's ability to work.
- Currently available beta interferons require self-injection once to four times each week. Self-injection can be painful and can lead to skin reactions and complications at injection sites so a treatment which reduces injection frequency is welcomed.
- The new medicine appears to have comparable efficacy at reducing relapse rates compared to current beta interferons, with consequent avoidance of residual disability. This is an established drug with a well-known risk/benefit profile and has less frequent injection frequency compared to presently available beta interferons leading to an improved quality of life, reduced steroid administration and potentially fewer hospital admissions.

Additional information: guidelines and protocols

The Association of British Neurologists published consensus guideline: Revised (2009) Guidelines for Prescribing in Multiple Sclerosis. These guidelines recommend treatment with interferon beta or glatiramer acetate in patients with relapsing remitting MS.[9]

NICE published clinical guideline 8: Multiple sclerosis: management of multiple sclerosis in primary and secondary care in November 2003, which recommends that patients with relapsing remitting MS should be offered interferon beta (any type) or glatiramer acetate within the 'risk sharing' scheme if the following criteria are met: can walk 100m or more without assistance; have had at least two clinically significant relapses in the last two years; are aged 18 years or older; and do not have any contraindications to treatment.[10]

The Health Technology Board for Scotland (HTBS) published the following statement in January 2002: The Health Technology Board for Scotland welcomes the Risk Sharing Scheme for beta interferons and glatiramer acetate, announced by the Scottish Executive. We are pleased that this is based on the National Institute for Clinical Excellence (NICE) recommendation to work with manufacturers to secure these medicines for patients in a cost effective manner. In light of the exceptional circumstances created by the Risk Sharing Scheme, HTBS and the Scottish Executive have agreed that HTBS will not provide a Comment on the NICE Technology Appraisal Guidance No 32: Beta interferons and glatiramer acetate for the treatment of multiple sclerosis. This decision was taken after careful

consideration of the needs of patients and health professionals in Scotland. As the Health Department Letter detailing the Risk Sharing Scheme addresses the implications for Scotland, we believe further authoritative advice in the form of an HTBS Comment is not only unnecessary, but may cause unhelpful confusion at this time. HTBS will work to ensure that the Scottish data from the Risk Sharing Scheme is taken into account in future advice to NHS Scotland on these treatments.[11]

Additional information: comparators

Interferon-beta-1a, interferon-beta-1b, glatiramer acetate, teriflunomide, fingolimod, dimethyl fumarate, alemtuzumab and natalizumab are all indicated for treatment of RRMS. However, alemtuzumab, fingolimod and natalizumab are indicated only for active or highly active RRMS.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Peginterferon-beta-1a	**125 micrograms SC every 2 weeks**	**8,502**
Alemtuzumab	12mg IV daily for 5 days (1st course) 12mg IV daily for 3 days (2nd course)*	35,225 (year 1) 21,135 (year 2)
Fingolimod	500 micrograms orally every day	19,084
Dimethyl fumarate	120mg to 240mg orally twice daily	17,836 to 17,849
Natalizumab	300mg IV every 4 weeks	14,690
Teriflunomide	14mg orally every day	13,492
Interferon-beta-1a (Rebif)	44 micrograms SC three times a week	10,572
Interferon-beta-1a (Avonex)	30 micrograms IM every week	8,502
Interferon-beta-1b (Betaferon)	250 micrograms SC on alternate days	7,240
Interferon-beta-1b (Extavia)	250 micrograms SC on alternate days	7,240
Glatiramer acetate	20 micrograms SC every day	6,682

* second course of alemtuzumab is administered one year after the first course. Doses are for general comparison and do not imply therapeutic equivalence. Cost of peginterferon-beta-1a from new product assessment form, costs of other medicines from MIMS on 17 September 2014. SC = subcutaneous; IM = intramuscular; IV = intravenous.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 7,529 in year 1 and 8,576 in year 5, with an estimated uptake rate of 0.2% (15 patients) in year 1 and 53.5% (4,588 patients) in year 5.

The gross impact on the medicines budget was estimated to be £128k in year 1 and £39.01m in year 5. As other medicines were assumed to be displaced, the net medicines budget impact is expected to be £4k in year 1 and £1.09m in year 5. The costs of the displaced medicines were estimated based on a weighted-average of the interferon-beta treatments only i.e. glatiramer was not included. However, it should be noted that these costs are based on the Risk Sharing Scheme prices for the comparator treatments.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Biogen Idec. Plegridy summary of product characteristics, accessed on 6.10.14.

2. European Medicines Agency. European public assessment report, Plegridy

3. Calabresi PA, Kieseier BC, Arnold DL et al. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. Lancet Neurol 2014; 13: 657–65.

4. Biogen Idec. Clinical study report for 105MS301 (ADVANCE).

5. Summary of product characteristics Avonex, accessed on 6.10.14

6. Summary of product characteristics Rebif, accessed on 6.10.14

7. Summary of product characteristics Betaferon, accessed on 6.10.14

8. Summary of product characteristics Extavia, accessed on 6.10.14

9. Association of British Neurologists consensus guideline revised (2009) Guidelines for Prescribing in Multiple Sclerosis

10. National Institute for Health and Care Excellence. Clinical guideline number 8: Multiple sclerosis: management of multiple sclerosis in primary and secondary care in November 2003.

11. Healthcare Improvement Scotland. Statement on the Risk Sharing Scheme for beta interferons and glatiramer acetate January 2002

This assessment is based on data submitted by the applicant company up to and including 13 October 2014.

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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.