

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Peginterferon beta-1a for treating relapsing– remitting multiple sclerosis

1 Recommendations

- 1.1 Peginterferon beta-1a is recommended, within its marketing authorisation, as an option for treating relapsing–remitting multiple sclerosis in adults.

Why the committee made these recommendations

Peginterferon beta-1a is an established drug for relapsing–remitting multiple sclerosis. There is clinical trial evidence showing that the drug slows disease progression and reduces the frequency of relapses when compared with placebo. There is also an indirect comparison suggesting that there are no differences in effectiveness when comparing peginterferon beta-1a with its main comparators, that is, other beta interferons and glatiramer acetate. However, it involves less frequent injections than other beta interferons, so improves choice for people with relapsing–remitting multiple sclerosis.

The cost-effectiveness estimates for peginterferon beta-1a compared with other treatments for relapsing–remitting multiple sclerosis, such as other beta interferons and glatiramer acetate, are in line with what NICE usually considers a cost-effective use of NHS resources. Therefore, peginterferon beta-1a can be recommended.

2 Information about peginterferon beta-1a

Marketing authorisation indication

- 2.1 Peginterferon beta-1a (Plegridy; Biogen Idec Ltd) has been licensed since 2014 'in adult patients for the treatment of relapsing remitting multiple sclerosis'.

Dosage in the marketing authorisation

2.2 Peginterferon beta-1a is given by subcutaneous injection every 2 weeks at a dose of 125 micrograms.

Price

2.3 The list price for peginterferon beta-1a is £654.00 per 2 pre-filled pens, each containing 125 micrograms (excluding VAT, BNF online, November 2019). Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Biogen, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with stakeholders. See the [committee papers](#) for full details of the evidence.

The committee was aware that several issues were resolved during the technical engagement stage. It agreed that the company had adequately justified some discrepancies in the company submission (both between the clinical- and cost-effectiveness sections, and when compared with previous appraisals).

The committee recognised that there were remaining areas of uncertainty associated with the analyses presented (see the technical report, table 2, page 36), and took these into account in its decision making. It discussed the following issues, which were outstanding after the technical engagement stage:

- issue 1: the population and appropriateness of comparators
- issue 2: the minimum clinically significant reduction in outcome measures
- issue 3: the generalisability of the ADVANCE trial population
- issue 5: treatment waning
- issue 6: stopping treatment for any reason
- issue 7: the utility values.

Treatment pathway

Any relapse can affect people with relapsing–remitting multiple sclerosis and is clinically significant

- 3.1 Relapsing–remitting multiple sclerosis is a chronic, disabling, lifelong neurological condition. People with the condition can have episodes of relapse, in which the symptoms worsen, followed by remission. However, over time, relapses result in worsening disability. The condition is associated with signs and symptoms such as pain, disturbance to muscle tone, chronic fatigue, unsteady gait, speech problems, incontinence, visual disturbance and cognitive impairment. The committee noted that reducing the frequency of relapses was a key outcome for people with the condition. It considered whether there was a clinically meaningful reduction in the number relapses. The patient and clinical experts explained that even 1 mild relapse can be devastating and can affect a person's family life and career. The committee concluded that any reduction in relapse was clinically significant.

Peginterferon beta-1a would most likely be offered first line or as an alternative first-line treatment when other options are not tolerated

- 3.2 Peginterferon beta-1a has been commissioned by NHS England since 2015 for people with relapsing–remitting multiple sclerosis as a first-line treatment or as an alternative when other first-line treatments are not tolerated. The committee noted that the licence is broader than this because it does not restrict peginterferon beta-1a to a particular line of therapy. It considered whether peginterferon beta-1a would also be of value in the more severe subgroups of 'highly active' and 'rapidly evolving severe' multiple sclerosis. The patient and clinical experts explained that peginterferon beta-1a would continue to be used primarily as a first-line treatment or as an alternative when other first-line treatments are not tolerated. They said that it would not be their first choice of treatment for people with more severe forms of relapsing–remitting multiple sclerosis. However, they stated that, in clinical practice, multiple sclerosis does not

lend itself to such clear categorisation. They also noted that patient choice is an important aspect of the treatment pathway, so they would not want to exclude use of peginterferon beta-1a later in the treatment pathway. For example, some people with more severe disease might prefer peginterferon beta-1a than other options if they were better able to tolerate it. The committee concluded that, in clinical practice, peginterferon beta-1a would likely continue to be used primarily as a first-line treatment or as an alternative when other first-line treatments are not tolerated. However, given the importance of patient choice, it agreed that any recommendation should not explicitly comment on its use later in the treatment pathway.

Other beta interferons and glatiramer acetate are the most relevant comparators

3.3 At the time of the committee discussion (November 2019), peginterferon beta-1a was already commissioned by NHS England as a first-line treatment option along with other beta interferons, dimethyl fumarate, glatiramer acetate, teriflunomide, alemtuzumab and ocrelizumab. The clinical experts explained that, of these, other beta interferons and glatiramer acetate were the most relevant comparators. Alemtuzumab and ocrelizumab are more active immunosuppressant treatments with a higher chance of more serious adverse effects, so would typically be used later in the treatment pathway. Also, as of November 2019, the Committee for Medicinal Products for Human Use recommended that the use of alemtuzumab should be restricted to 'relapsing–remitting multiple sclerosis that is highly active despite adequate treatment with at least one disease-modifying therapy or if the disease is worsening rapidly with at least two disabling relapses in a year and brain-imaging showing new damage'. The committee concluded that alemtuzumab and ocrelizumab were not relevant comparators at the place in the pathway where people were most likely to use peginterferon beta-1a.

Peginterferon beta-1a offers a less frequent dosing schedule, helping with patient choice

3.4 The committee considered how people would choose between the several beta interferons available. The patient and clinical experts explained that, if a treatment with 1 beta interferon had failed, another would not typically be offered. They stated that peginterferon beta-1a is not considered to be more effective than other beta interferons but has a less frequent dosing schedule. It is administered twice monthly, whereas other beta interferons may need to be administered as often as 3 times a week. The clinical experts stated that people were less likely to develop neutralising antibodies with peginterferon beta-1a than with other interferons. However, the committee was not shown data to support this and questioned its relevance. One clinical expert explained that, when offering a choice of treatments, clinicians generally remain neutral to allow people to choose the best treatment for their lifestyle. For example, some people prefer the reduced dosing schedule of peginterferon beta-1a, whereas others, such as those with cognitive issues affecting memory, might prefer a more frequent, regular schedule. The committee concluded that the availability of peginterferon beta-1a increased patient choice.

Clinical effectiveness

The ADVANCE trial has issues with generalisability, but is appropriate for decision making

3.5 The company presented the evidence for peginterferon beta-1a from:

- ADVANCE, a phase 3 double-blind randomised placebo-controlled trial and
- ATTAIN, a 2-year blinded follow-up study (of peginterferon beta-1a only; all people in the placebo arm of ADVANCE switched to peginterferon beta-1a after 1 year).

The ADVANCE trial recruited patients mainly from the eastern

European region, and included only 8% from western Europe (of which 14 patients were from the UK). The ERG explained that there were some numerical differences in effectiveness across regions, with region 1 (which included the UK) performing the worst. However, the company stated that it did not find statistical interaction by region. The patient and clinical experts explained that any patients from the UK in the trial were likely not typical of those seen in NHS clinical practice. This was because, given the many active treatments available on the NHS, there would be little incentive for people with multiple sclerosis to join a placebo-controlled trial. Also, there may be differences in clinical practice, treatments and standard of care across regions. The committee agreed that all these factors raised questions around how representative the trial would be of a UK population. However, it noted that most patients in the trial were treatment naive (the expected place in the treatment pathway for peginterferon beta-1a). It also noted that, if there were any differences in the population, this was unlikely to have had an impact on the treatment effect of peginterferon beta-1a compared with placebo. The committee concluded that it had minor concerns about the generalisability of the ADVANCE and ATTAIN trials. However, overall, it considered that they were appropriate for decision making.

It is disappointing that there is no evidence to help address gaps in evidence on areas such as generalisability, treatment waning and stopping treatment

3.6 Given its concerns about generalisability, the committee considered whether there was any pharmacoepidemiologic evidence available from current use of peginterferon beta-1a in the NHS. The company explained that, of around 12,000 people in the UK currently using injectable treatments for relapsing–remitting multiple sclerosis, about 1,400 use peginterferon beta-1a. The committee stated that, if the company had provided data on these patients, it would have helped inform evidence gaps in areas such as generalisability (see section 3.5), stopping treatment (section 3.13) and treatment waning (section 3.14). It was

disappointed that it had not been presented with this evidence, which could have helped to address these evidence gaps.

Peginterferon beta-1a is clinically effective when compared with placebo

3.7 In ADVANCE, there were statistically significant ($p < 0.05$) improvements with peginterferon beta-1a compared with placebo for the primary outcome (annualised relapse rate) and several important secondary outcomes, including disability progression sustained for 3 or 6 months:

- annualised relapse rate: rate ratio 0.64 (0.50 to 0.83; $p = 0.0007$)
- confirmed disability progression at 3 months: hazard ratio: 0.62 (0.40 to 0.97; $p = 0.04$)
- confirmed disability progression at 6 months: hazard ratio: 0.46 (0.26 to 0.81; $p = 0.007$).

The committee agreed that there had been improvements in important outcomes such as relapse frequency when compared with placebo. It also noted its previous conclusion that any reduction in the frequency of relapses was clinically significant (see section 3.1). The committee concluded that peginterferon beta-1a was both a clinically and statistically significantly effective treatment when compared with placebo.

Peginterferon beta-1a does not appear to be more effective than its main comparators in an indirect comparison with active treatments

3.8 Because there was no direct trial evidence comparing peginterferon beta-1a with active comparators, the company also conducted indirect analyses comparing it with the other beta interferons, dimethyl fumarate, glatiramer acetate, teriflunomide, alemtuzumab and ocrelizumab. Several of the results are academic-in-confidence and cannot be presented here. However, overall, the committee concluded that there were no statistically significant differences for peginterferon beta-1a compared with its main comparators (that is, other beta interferons and glatiramer acetate).

Adverse events

Peginterferon beta-1a is an established treatment with a well-known side effect profile

3.9 The patient and clinical experts explained that the most common adverse events were injection-site reactions and flu-like symptoms. Although these could sometimes be severe, they were generally mild to moderate and easily treatable with common analgesics such as paracetamol and ibuprofen. The experts were not aware of any differences in adverse effects between the beta interferons. The committee concluded that peginterferon beta-1a is an established treatment with a well-known side effect profile.

The company's economic model

The company's economic model structure is appropriate for the decision making

3.10 The company estimated disease progression in the model using 21 health states. It defined these using Expanded Disability Status Scale (EDSS) scores ranging from 0 to 9.5 (with a higher score indicating worse disease) and either relapsing–remitting or secondary progressive multiple sclerosis, plus a death state. In each cycle of the model, a patient with relapsing–remitting multiple sclerosis could move to a higher or lower EDSS state (that is, their disability could worsen or improve) or remain in the same state. The disease could also advance from relapsing–remitting multiple sclerosis to secondary progressive multiple sclerosis, but could not then move back to relapsing–remitting disease. The clinical experts explained that it was not realistic to assume that patients could not improve from secondary progressive to relapsing–remitting MS. Also, the company assumed that, once treatment with peginterferon beta-1a stopped, a patient's condition followed the untreated natural history of the disease. However, in clinical practice, people would have several other treatments to choose from. The company stated it had chosen not to

include any treatment sequencing because it could have biased the model, making it unclear whether any observed treatment effect was coming from the main intervention or the next line of treatment. The committee agreed with this approach. It noted that the overall structure of the company's model was similar to models used in previous NICE technology appraisals for the first-line treatment of relapsing–remitting MS. The committee concluded that the structure of the company's economic model was appropriate for decision making.

The baseline population should be based on the MS risk sharing scheme

3.11 The company used the characteristics of patients in the ADVANCE trial to reflect the baseline population in the model. The committee discussed whether ADVANCE was the most appropriate source, given its earlier minor concerns that there were issues with generalisability in the trial (see section 3.5). It was aware that models in some previous appraisals for this disease area had used the MS risk sharing scheme (RSS) as the source for its baseline population. The RSS collected data for more than 5,000 patients in the NHS for over 10 years. The committee agreed that this population in the RSS was more generalisable to the NHS than the population in ADVANCE. It concluded that it would have preferred that the model baseline characteristics had been based on the RSS.

Utility values in the economic model

Utility values are a source of uncertainty in the model

3.12 The company used utility values from Orme et al. (2007) for consistency with previous technology appraisals. It also provided utility values from a more recent study, Thompson et al. (2017). The ERG provided a scenario analysis using Thompson et al. (2017). The committee noted that the utility values in both Thompson et al. and Orme et al. were very similar. However, it noted that there were substantial differences in the quality adjusted life years generated by the deterministic and probabilistic models. This was unusual and could suggest that there may have been

an issue with the underlying utility values used in the model. The committee discussed whether it could identify any underlying problems with the utility values. The company did not adjust utility values to worsen with age, which the committee agreed was unrealistic. It also noted that older people were more likely to be in a higher EDSS score group in the model (in which higher EDSS scores were associated with a worse utility value), and that the Orme et al. and Thompson et al. studies differed with respect to age, which could have led to different model predictions. The committee agreed that, because the utility values seemed to be a key driver of cost effectiveness in the model, the company should have explored this more thoroughly, for example, by using values derived from a meta-analysis. The committee concluded that the utility values were a source of uncertainty in the cost-effectiveness results.

Assumptions in the economic model

There is lack of robust data about the individual stopping rules

3.13 The company applied a probability of stopping treatment for any reason in its base-case analysis. It used the annualised stopping rates from 18 trials. It weighted these based on sample size to derive the risk of stopping treatment for any reason for each disease-modifying therapy. The ERG considered that deriving the stopping risk weighted by person time would be more appropriate than using the trial sample size. This was because an annualised stopping rate would not capture changes over time. The company accepted this correction. However, the ERG stated that it would have preferred the use of a 5% stopping rule across all treatments, which was derived from the MS RSS. The committee agreed that it was more likely that different treatments would have different stopping rates. It also noted that data on treatment-specific stopping rates in the UK should be available because they are recorded electronically on NHS payment systems. It was disappointed that these had not been presented. The committee concluded that, in the absence of the actual

data, it was more plausible to assume a treatment-specific rate than a flat rate.

The treatment effect waning cannot be estimated precisely because of a lack of evidence

3.14 The company assumed in the model that the treatment effect of all treatments waned over time, and all at the same rate. This was in line with NICE's technology appraisals on [beta interferons and glatiramer acetate](#) and [ocrelizumab](#):

- years 1 and 2: no waning
- years 3 to 5: 75% of full treatment effect
- year 6 onwards: 50% of full treatment effect.

The clinical experts stated that most treatments for multiple sclerosis become less effective over time. This is either because the person's immune system develops neutralising antibodies, or because the condition worsens and becomes resistant to treatment. It was unclear whether the treatment effect waning with peginterferon beta-1a would differ from other treatments. The committee noted that peginterferon beta-1a is an established treatment and that data on treatment effect waning could have been collated. However, the company had not attempted to analyse whether the treatment effect of peginterferon beta-1a changed over time, which left an important gap in the evidence. The committee concluded that it was appropriate to include some treatment effect waning in the model, and that it would have been more plausible to assume treatment-specific rates rather than a constant rate. However, the committee noted that varying this assumption (that is, using a constant rate for all treatments, or varying the rate by treatment) did not substantially affect cost-effectiveness results. Because of this, the committee accepted the company's base-case assumption.

ERG's changes to the assumptions in the economic model

Both the company and ERG cost-effectiveness results are considered in the decision making

3.15 The ERG made several changes to the company's base case. It stated that the most important of these were:

- changing the treatment-specific stopping rates to a flat rate of 5% from the MS RSS (because it considered these data more informative than trial data for the outcome of stopping treatment) and
- the source of decrements in the utility of caregivers (because its preferred source assumed utility decrements rose with worsening health state).

The committee agreed with some, but not all, of the ERG changes. For example, it agreed that caregiver utility decrements should rise with worsening EDSS health state, and that the company should have used the baseline population from the RSS rather than the trial. However, it disagreed that it was more plausible to assume a constant stopping rate for all treatments than a treatment-specific rate. The committee concluded it would take into account the various company and ERG base cases and scenarios in its decision making.

Cost-effectiveness estimate

Peginterferon beta-1a is an established NHS treatment and a cost-effective use of NHS resources

3.16 The committee agreed that enough evidence had been presented to consider the cost effectiveness of peginterferon beta-1a. However, given the number of years that peginterferon beta-1a has been an established treatment in the NHS, it was disappointed that the company had not provided data reflecting the experience with peginterferon-1a in NHS practice. This data would have helped to address uncertainty in the

model, including for stopping rates and treatment waning. The ERG and company presented a number of exploratory analyses that did, in part, helped to reduce some of these uncertainties. Results of all these analyses suggested that the incremental cost-effectiveness results of peginterferon beta-1a were in the range that NICE normally considers a cost-effective use of NHS resources. The results are commercial in confidence because of confidential comparator patient access schemes, so cannot be reported here.

4 Implementation

- 4.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has relapsing–remitting multiple sclerosis and the doctor responsible for their care thinks that peginterferon beta-1a is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Review of guidance

- 5.1 The guidance on this technology will be considered for review 3 years after publication. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler

Chair, appraisal committee

January 2020

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4-technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee B](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes](#) of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Irina Voicechovskaja and Sharlene Ting

Technical lead

Carl Prescott

Technical adviser

Jeremy Powell

Project manager

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