

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Appraisal consultation document

**Beta interferons and glatiramer acetate for
treating multiple sclerosis**

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using beta interferons and glatiramer acetate in the NHS in England. The appraisal committee has considered the evidence submitted and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the [committee papers](#)).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on these technologies. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination.
- Subject to any appeal by consultees, the final appraisal determination may be used as the basis for NICE's guidance on using beta interferons and glatiramer acetate in the NHS in England.

For further details, see NICE's [guide to the processes of technology appraisal](#).

The key dates for this appraisal are:

Closing date for comments: 24/01/2018

Fourth appraisal committee meeting: 6 March 2018

Details of membership of the appraisal committee are given in section 8.

1 Recommendations

- 1.1 Extavia (interferon beta 1b) is recommended as an option for treating multiple sclerosis, only if:
- the person has relapsing–remitting multiple sclerosis or
 - the person has secondary progressive multiple sclerosis with continued relapses and
 - the company provides it with the discount agreed in the patient access scheme.
- 1.2 Glatiramer acetate, Avonex and Rebif (both interferon beta 1a), Betaferon (interferon beta 1b) and Plegridy (pegylated interferon beta 1a) are not recommended within their marketing authorisations as options for treating multiple sclerosis.
- 1.3 These recommendations are not intended to affect treatment with glatiramer acetate or a beta interferon that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. This decision should be made jointly by the clinician and the child or young person, and the child's or young person's parents or carers.

Why the committee made these recommendations

Evidence from clinical trials and the Department of Health's Risk Sharing Scheme shows that glatiramer acetate and the beta interferons are effective for treating multiple sclerosis. It also shows that all the treatments work similarly in slowing progression to disability and in reducing the number of multiple sclerosis-related relapses.

The cost-effectiveness estimate for Extavia, a beta interferon, compared with best supportive care is within the range that NICE usually considers a cost-effective use of NHS resources. So, Extavia is recommended as an option for treating multiple

sclerosis. Glatiramer acetate and the other beta interferons (Avonex, Betaferon, Plegridy and Rebif) are more expensive than Extavia, and the most likely cost-effectiveness estimates for these treatments compared with best supportive care are higher than what NICE normally considers acceptable. So, these treatments are not recommended for multiple sclerosis because they would not be a good use of limited NHS resources at their current prices.

No recommendation was made for clinically isolated syndrome because its definition has changed and it is uncertain whether it will remain a clinically distinct condition in the future.

2 Information about interferon beta 1a, interferon beta 1b, pegylated interferon beta 1a and glatiramer acetate

<p>Marketing authorisation indications</p>	<p>Avonex (interferon beta 1a) is licensed for the treatment of ‘patients diagnosed with relapsing multiple sclerosis’. In clinical trials, ‘this was characterised by two or more acute exacerbations (relapses) in the previous three years without evidence of continuous progression between relapses’. It is also licensed for the 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’.</p> <p>Rebif (interferon beta 1a) is licensed for the treatment of ‘patients with relapsing multiple sclerosis. In clinical trials, this was characterised by two or more acute exacerbations in the previous two years’. It is also licensed for the treatment of ‘patients with a single demyelinating event with an active inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis’.</p> <p>Plegridy (interferon beta 1b) is licensed 'in adult patients for the treatment of relapsing remitting multiple sclerosis’.</p> <p>Betaferon (interferon beta 1b) and Extavia (pegylated interferon beta 1a) are licensed for the treatment of ‘patients with relapsing-remitting multiple sclerosis and two or more relapses within the last two years’. They are also licensed for the 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’. They are also licensed for the treatment of ‘patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses’.</p> <p>Glatiramer acetate is licensed for ‘the treatment of relapsing forms of multiple sclerosis’. It is not indicated in primary or secondary progressive multiple sclerosis.</p>
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Dosages in the marketing authorisations	<p>Avonex is given by intramuscular injection weekly at a dose of 30 micrograms.</p> <p>Rebif is given by subcutaneous injection 3 times per week at a dose of 44 or 22 micrograms.</p> <p>Plegridy is given by subcutaneous injection every 2 weeks at a dose of 125 micrograms.</p> <p>Betaferon and Extavia are given by subcutaneous injection every other day at a dose of 250 micrograms.</p> <p>Glatiramer acetate is given by subcutaneous injection once daily at a dose of 20 milligrams or 3 times a week at a dose of 40 milligrams.</p> <p>See the summaries of product characteristics for full dosage schedules.</p>
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<p>Prices</p>	<p>The list price for Avonex is £163.50 per pre-filled pen containing 30 micrograms (excluding VAT, British National Formulary [BNF] online, November 2017).</p> <p>The list price for Rebif is £51.13 per pre-filled syringe containing 22 micrograms or £67.77 per pre-filled syringe containing 44 micrograms (excluding VAT, BNF online, November 2017).</p> <p>The list price for Betaferon and Extavia is £39.78 per vial containing 300 micrograms (excluding VAT, BNF online, November 2017).</p> <p>The list price for Plegridy is £327.00 per pre-filled pen containing 125 micrograms (excluding VAT, BNF online, November 2017).</p> <p>The list price for glatiramer acetate is £18.36 per pre-filled syringe containing 20 milligrams or £42.83 per pre-filled syringe containing 40 milligrams (excluding VAT, BNF online, November 2017).</p> <p>Costs may vary in different settings because of negotiated procurement discounts.</p> <p>Two companies have agreed patient access schemes with the Department of Health. The levels of the discount are commercial in confidence. One of these schemes provides a simple discount to the list price of Extavia with the discounts applied at the point of purchase or invoice. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS. With the other scheme, if Rebif had been recommended, it would provide a simple discount to the list price of Rebif with the discount applied at the point of purchase or invoice. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.</p> <p>One company has agreed a nationally available price reduction with the Commercial Medicines Unit. This makes glatiramer acetate available at a reduced cost. The contract price agreed through the framework is commercial in confidence.</p>
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3 Committee discussion

The appraisal committee (section 6) considered evidence from a number of sources. See the [committee papers](#) for full details of the evidence.

Remit and objective of this appraisal

This appraisal is a review of NICE technology appraisal guidance on beta interferons and glatiramer acetate for the treatment of multiple sclerosis

3.1 NICE's original technology appraisal guidance on beta interferons and glatiramer acetate for the treatment of multiple sclerosis considered that these technologies were more clinically effective than best supportive care, but were not a cost-effective use of NHS resources. The Department of Health then established a Risk Sharing Scheme (RSS), which provided the drugs to patients in the NHS and monitored their effectiveness. The scheme was set up so that if the drugs were less effective than anticipated, the prices would fall. Because the RSS has now ended, NICE is again appraising these drugs. All patients with relapsing–remitting or secondary progressive multiple sclerosis with relapses who are able to walk were eligible for treatment under the RSS. The scheme did not include people with clinically isolated syndrome or primary progressive multiple sclerosis. The committee understood that the RSS did not include treatment with Plegridy or Extavia, but noted that Extavia is the same as Betaferon.

This appraisal compares beta interferons and glatiramer acetate with best supportive care

3.2 Since NICE originally appraised these drugs, it has recommended other treatment options for relapsing–remitting multiple sclerosis including [alemtuzumab](#), [cladribine](#), [daclizumab](#), [dimethyl fumarate](#) and [teriflunomide](#). These appraisals generally compared the newer drugs with the older beta interferons and glatiramer acetate, under the assumption that the older drugs were provided to the NHS in a cost-effective way through the RSS. The committee understood that its remit was to revisit the original appraisal, and to compare beta interferons and glatiramer acetate with best supportive care, rather than with the newer drugs.

The condition and current treatment pathway

Multiple sclerosis is a chronic, disabling neurological condition

- 3.3 The clinical and patient experts stated that multiple sclerosis is a chronic, disabling neurological condition. The patient experts explained that relapsing–remitting multiple sclerosis can limit people’s ability to work, and to engage in social and family life. Having a wide range of first-line treatments increases the chance of finding a treatment that works in a given patient for this complex disease, and most patients try at least 1 course of a beta interferon or glatiramer acetate before moving on to other therapies. People whose disease progresses from relapsing–remitting multiple sclerosis to secondary progressive multiple sclerosis, but who continue to have relapses, may continue to have beta interferon. The committee understood that people have treatment until they can no longer walk, when they stop treatment.

Clinical effectiveness in clinically isolated syndrome

The relevance of clinically isolated syndrome for this appraisal is unclear

- 3.4 A single demyelinating event is known as clinically isolated syndrome, and people experiencing this have a high chance of developing multiple sclerosis. The clinical experts stated that the diagnostic criteria for multiple sclerosis changed in 2010. Clinically isolated syndrome is no longer as relevant as it once was, and about half of people previously considered to have the condition are now considered to have multiple sclerosis. Increasingly, MRI evidence is used to diagnose multiple sclerosis at an earlier stage. People with clinically isolated syndrome who go on to need treatment are then considered to have multiple sclerosis. The diagnostic criteria will soon be revised again, which may mean that clinically isolated syndrome as currently defined will cease to exist. The assessment group conducted a network meta-analysis for clinically isolated syndrome, which included 5 trials. The companies did not include clinically isolated syndrome in their meta-analyses, and people with clinically isolated

syndrome were not included in the RSS. The committee noted that all the treatments delayed time to clinically definite multiple sclerosis as it was then defined compared with placebo. However, the committee considered that the clinical trials using the older definition were not generalisable to current UK practice. It acknowledged that, although clinically isolated syndrome was included in NICE's final scope, the treatment pathway had evolved. The committee was unable to define the population or the purpose of treatment, and did not further consider clinically isolated syndrome.

Clinical effectiveness in relapsing–remitting multiple sclerosis

Evidence from clinical trials and the RSS were considered

3.5 The committee considered evidence from 4 network meta-analyses of clinical trials from:

- the assessment group
- Biogen (Avonex, interferon beta-1a; Plegridy, pegylated interferon beta-1a)
- Merck Serono (Rebif, interferon beta-1a)
- Teva (glatiramer acetate).

In addition to the data from clinical trials, the committee also considered data collected from patients participating in the RSS, provided by the Department of Health.

Clinical trials

The trials were broadly generalisable but subject to bias

3.6 The committee considered the generalisability of the clinical trials to patients in the NHS. The assessment group stated that the trials including people with relapsing–remitting multiple sclerosis had limitations including differences in design and short length of follow-up, and were at risk of bias because injection-site reactions could mean that patients in the trials were not blinded to their treatment. The clinical experts stated that unblinding

was unlikely to bias the results for disability progression, which was assessed by investigators blinded to treatment allocation. It concluded that the trials were broadly generalisable and relevant for this appraisal.

Disability progression outcome measure

Trial data for confirmed disability progression sustained for 6 months was preferred

3.7 The committee discussed whether disability progression sustained for 3 months or for 6 months best reflected disability progression in people with relapsing–remitting multiple sclerosis. It recognised that some trials provided both 3- and 6-month data, and that all trials reported 3-month data. It was aware that, in previous appraisals, the committee preferred to use confirmed disability progression for 6 months. The clinical experts explained that the time taken to recover from a relapse can vary and that people may still continue to recover after 3 months. The committee agreed that the outcome for confirmed disability progression sustained for 6 months was better at capturing the benefits of treatment. The assessment group stated that it preferred to use confirmed progression at 3 months because the quality and size of its evidence network at this time point was better than that for a confirmed progression at 6 months. The committee concluded that it preferred 6-month data where available, but that it was important to use a consistent measure across all treatments.

Companies' and assessment group's network meta-analyses

The assessment group's network meta-analysis was preferred

3.8 The assessment group stated that some of the companies' meta-analyses had limitations, including, but not limited to, methods that were not transparent or analyses that did not include relevant trials. The committee also noted that the point estimates for the results broadly corresponded to results from the assessment group's network meta-analysis (see section 3.9). However, the companies' analyses had wider statistical intervals and showed fewer statistically significant differences between

technologies. The assessment group stated that it used a frequentist approach for its meta-analysis, whereas the companies used a Bayesian approach. The committee agreed that this could explain some of the differences in results between the assessment group's and companies' analyses. The committee agreed to focus on the assessment group's network meta-analyses.

Results of assessment group's network meta-analysis

All treatments were similarly effective in reducing the number of relapses and slowing disability progression compared with placebo

3.9 The committee considered the results of the network meta-analysis (see table 1) by outcome for people with relapsing–remitting multiple sclerosis.

- **Annualised relapse rate:** all the beta interferons and glatiramer acetate reduced the annualised relapse rate compared with placebo. When comparing each of the beta interferons and glatiramer acetate with each other, the results did not show that any one was better. The clinical experts considered the drugs under appraisal to be broadly similar in clinical effectiveness. The committee concluded that all the therapies were similarly effective in reducing the number of relapses compared with best supportive care.
- **Confirmed disability progression:** the treatments delayed disability compared with placebo but did not differ from each other. The committee concluded that the beta interferons and glatiramer acetate had similar effectiveness, and that they all delayed disability progression when compared with placebo.
- **Adverse events:** the committee considered the risk of stopping treatment because of adverse events. It noted that all the treatments were associated with more adverse events than placebo. It also noted that, although some of the drugs were associated with a higher risk of adverse events than others, the confidence intervals surrounding these estimates were very large. Beta interferons and glatiramer

acetate have well-established safety profiles. The committee concluded that all the drugs would cause some adverse events.

Table 1 Results from the assessment group’s network meta-analysis for relapsing–remitting multiple sclerosis

Drug	ARR RR (95% CI)	TTP3 HR (95% CI)	TTP6 HR (95% CI)	AEs RiR (95%CI)
IFN beta-1a pegylated 125 micrograms every 2 weeks	0.64 (0.50, 0.83)	0.62 (0.40, 0.97)	0.46 (0.26, 0.81)	-
Glatiramer 40 mg 3 times weekly	0.66 (0.54, 0.80)	-	-	-
Glatiramer 20 mg daily	0.68 (0.61, 0.75)	0.76 (0.60, 0.97)	0.82 (0.53, 1.26)	2.60 (0.88, 7.64)
IFN beta-1a 44 micrograms 3 times weekly	0.68 (0.61, 0.76)	0.63 (0.46, 0.86)	0.47 (0.24, 0.93)	3.85 (0.81, 18.29)
IFN beta-1b 250 micrograms every other day	0.70 (0.63, 0.77)	0.78 (0.59, 1.02)	0.34 (0.18, 0.63)	4.41 (1.07, 18.29)
IFN beta-1a 22 micrograms 3 times a week	0.72 (0.62, 0.85)	0.68 (0.49, 0.96)	-	1.86 (0.21, 16.83)
IFN beta-1a 30 micrograms weekly	0.80 (0.73, 0.89)	0.73 (0.53, 1.00)	0.68 (0.49, 0.94)	1.61 (0.52, 5.02)

All drugs compared with placebo.
Abbreviations: AEs, stopping treatment because of adverse events at 24 months; ARR, annualised relapse rate; CI, confidence interval; HR, hazard ratio; IFN, interferon; RiR, risk ratio; RR, rate ratio; TTP3, time to disability progression confirmed at 3 months; TTP6, time to disability progression confirmed at 6 months.

Risk Sharing Scheme

RSS data are more likely to reflect effectiveness in clinical practice than data from the clinical trials

3.10 The committee discussed the RSS, which included NHS patients treated with either a beta interferon or glatiramer acetate. It noted that the RSS did not include some of the technologies in this appraisal (that is, Plegridy and Extavia), which were licensed after the scheme started. A representative from the RSS stated that the scheme included a large

number of people and ran for 10 years (the Department of Health considered the number of people and the average length of follow-up as confidential). The committee recognised that the RSS provided longer follow-up than the trials, and that it reflected the people who would be offered these therapies in NHS practice. It concluded that it preferred the effectiveness data from the RSS.

The RSS used a summary measure of disease progression as its primary outcome

3.11 The primary outcome measuring effectiveness in the RSS was the change over time relative to baseline of a weighted sum of the proportions of patients who progressed to each Expanded Disability Status Scale (EDSS) score. This was weighted by utility, to account for the non-linearity of the EDSS scale (that is, for example, a change in EDSS from 0 to 1 does not have the same impact as a change from 8 to 9). The Department of Health stated that to use the outcome measure of the RSS it was necessary to derive an ‘implied’ hazard ratio. The Department of Health used data reflecting the natural history of disease in people not taking disease-modifying treatments from the British Columbia Multiple Sclerosis cohort for comparison because there was no comparator in the RSS (that is, nobody had best supportive care). People in the RSS were matched to people in the historical cohort by EDSS score and age of onset. A hazard ratio for disease progression was applied to progression probabilities in the British Columbia cohort to derive the progression probabilities for people in the RSS. This ‘implied’ hazard ratio was derived to obtain the same change in mean utility between baseline and year 10 as that seen in the RSS cohort. The committee agreed that the ‘implied’ hazard ratio represented the relative effectiveness of the treatments in slowing disease progression as seen in the RSS when compared with that expected from people in the British Columbia Multiple Sclerosis cohort on supportive care.

All treatments in the RSS slowed disease progression

3.12 The pooled implied hazard ratio (the value is not directly comparable with the trial-based hazard ratios) showed that the treatments delayed disease progression compared with best supportive care (hazard ratio 0.79; 95% confidence interval 0.77 to 0.81). The Department of Health has indicated that the hazard ratios for individual drugs are confidential, and that all showed a fairly similar delay in disease progression compared with best supportive care. The committee concluded that, consistent with the data from trials, all the technologies offered in the RSS delayed disease progression compared with best supportive care.

Pooled RSS estimates are preferable

3.13 The assessment group used the pooled effectiveness estimates in its base-case analyses, rather than the results for the individual technologies from the RSS. The committee agreed that this was appropriate because:

- The network meta-analysis results did not show that any particular beta interferon or glatiramer acetate was better than another (see section 3.9).
- Data for each individual technology in the RSS could be subject to selection bias. That is, because people in the RSS were not randomised to a specific treatment, the treatment decision, and therefore the outcomes, may have been affected by differences in the patient characteristics.
- The pooled analysis from the RSS included people who switched to another treatment, whereas people who switched were excluded from the analyses for individual treatments. The committee considered that, although few people switched treatments, people who do switch may have a worse prognosis than those who do not. This means that the hazard ratios are lower (that is, the treatments appear more effective) in the analyses for the individual treatments than in the pooled analysis.

The committee concluded that it would use the RSS estimates representing the pooled effect in its decision-making.

Pooled RSS estimates should also be used for Extavia and Plegridy

3.14 Not all the technologies were made available on the RSS (that is, Plegridy and Extavia were not included in the RSS). The committee understood that Extavia was the same as Betaferon, which the RSS included. The committee concluded that it was appropriate to assume that the effectiveness of Extavia was the same as that of Betaferon in the RSS. It recalled that the network meta-analysis results did not show that Plegridy, nor any particular beta interferon or glatiramer acetate, was conclusively better than another (see section 3.9). The committee was also aware that the evidence for Plegridy was based on 1 trial. It noted that this trial was subject to the biases identified for other trials (see section 3.6). The committee concluded that, for modelling, it was appropriate to generalise the pooled RSS data on the interferons and glatiramer acetate to Plegridy.

Waning of treatment efficacy

Efficacy does not remain constant over time

3.15 The committee discussed whether the effectiveness of beta interferons and glatiramer acetate was likely to remain constant or wane over time. The clinical experts stated that most treatments for multiple sclerosis become less effective over time, either because the person's immune system develops neutralising antibodies or because the disease worsens and becomes resistant to treatment. The Department of Health stated that, in the RSS, the effect of the treatments waned after the first 2 years. The committee concluded that, for decision-making, it was appropriate to assume that efficacy does not remain constant over time.

Cost effectiveness in relapsing–remitting multiple sclerosis

NICE received versions of the RSS model from 5 sources

3.16 The committee discussed the economic models and modelling assumptions for relapsing–remitting multiple sclerosis from 5 sources:

3 companies (Biogen, Merck Serono and Teva), the assessment group and the Department of Health:

- The Department of Health provided the RSS model to the assessment group. The overall structure of all submitted models was the same and similar to models used in previous NICE technology appraisals. The sources of data used as model inputs differed across the models.
- All models estimated disease progression through 21 health states defined by EDSS scores (ranging from 0 to 9.5). The models described the progression of disability in patients with relapsing–remitting multiple sclerosis (10 states) to secondary progressive multiple sclerosis (10 states) and to death.
- 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 committee appreciated that the treatments increased quality-adjusted life years (QALYs) relative to best supportive care primarily by delaying disability progression and also by reducing the number of relapses. The model also incorporated EDSS-related (and other) mortality and therefore the treatments also increased life expectancy.
- The treatment effect used in the models varied, representing either pooled or individual treatment estimates for effectiveness from either the RSS or from network meta-analyses of trials.
- The assessment group model included the assumption that 5% of patients per year stop treatment; this was equal across all the treatments, and was based on what had been seen in the RSS.
- The assessment group had changed the assumptions about mortality in the RSS model to avoid double-counting of multiple sclerosis-related mortality (see section 3.19).

Natural history of the disease in subgroup analyses

The RSS used an historical cohort as a comparator

3.17 The RSS model used a database from British Columbia to reflect the natural history of multiple sclerosis for people who do not have disease-modifying treatments. The RSS model had originally used a database from London Ontario instead, but this did not include the possibility that patients' EDSS scores could improve, whereas EDSS scores for patients treated with disease-modifying drugs in the RSS did improve. The committee was aware that the British Columbia dataset was relatively old, having begun in 1980, and that supportive care may have since changed. However, it was also aware that the alternative dataset, London Ontario, was even older and was also smaller. The committee concluded that it was appropriate to use the British Columbia database to model the natural history of multiple sclerosis for people who had not had disease-modifying treatments.

Time horizon and waning of treatment effect

The approach to effectiveness waning over time varied from previous appraisals

3.18 The assessment group, Department of Health and the companies chose a time horizon of 50 years for their base-case analyses. The committee agreed that this was long enough to reflect a lifetime horizon, and noted the uncertainties about extrapolating over a lifetime. It also noted that the RSS model assumed a waning effect, with an 'arbitrary' 50% reduction in effect after 10 years. NICE's previous technology appraisals (such as [alemtuzumab for treating relapsing–remitting multiple sclerosis](#) and [dimethyl fumarate for treating relapsing-remitting multiple sclerosis](#)) assumed a reduction in treatment effect of 25% after 2 years and of 50% after 5 years. The committee considered that it was appropriate to use a different assumption for the waning effect in this appraisal, as the RSS provided longer follow-up than the trials in the previous appraisals. The

committee concluded that assuming a 50% reduction in effect after 10 years was appropriate.

Mortality

The standardised mortality ratios in Pokorski (1997) overestimate mortality risk in patients with multiple sclerosis

3.19 In the original RSS model, mortality was included in 2 ways. First, the model included multiple sclerosis-related mortality for all transitions to EDSS health state 10. Second, the model included an increased risk of mortality to account for the increased risk of non-multiple sclerosis-related death in people with multiple sclerosis. The assessment group was concerned that this approach double-counted mortality and so removed the increased risk of mortality from non-multiple sclerosis-related causes from its analysis. An alternative approach was suggested by Merck Serono. This applied mortality ratios from Pokorski to each EDSS health state, which resulted in a greater risk of mortality in people with multiple sclerosis than in the original RSS approach and the assessment group's approach. The committee was concerned that Pokorski overestimated mortality, particularly for lower EDSS states, as it was based on outdated data from a period before there had been improvements in multiple sclerosis care and when smoking prevalence was greater. It was also concerned that, in the study, EDSS was only measured at the first clinical visit but that the actual EDSS score at time of death depended on the speed of EDSS progression. The committee noted that, although similar approaches based on Pokorski had been used in several previous NICE appraisals ([fingolimod](#), [teriflunomide](#), [alemtuzumab](#) and [daclizumab](#)), the latest appraisal for [cladribine](#) used a more recent study with lower mortality (Jick et al., 2014). The committee agreed that the approach using Pokorski had limitations and overestimated mortality, and would have preferred to see analyses using Jick as an alternative to the assessment group's approach. It concluded that this was a source of uncertainty but accepted the approach taken by the assessment group.

Treatment stopping rates

Stopping rates from the RSS are appropriate for use in the economic model

3.20 In its model, the assessment group included stopping rates from the RSS, in which 5% of people stopped treatment each year. The Department of Health stated that stopping rates were similar across treatments. Biogen had concerns that the stopping rates assumed for beta interferons in NICE's technology appraisal of daclizumab were higher (about 10% each year). The committee was aware that the daclizumab appraisal focused on a more severe form of multiple sclerosis (that is, rapidly-evolving severe multiple sclerosis and multiple sclerosis that has been previously treated with disease-modifying therapy) and concluded that for this appraisal it was appropriate to use data from the RSS.

Utility values

Disutility to carers should be considered

3.21 The committee discussed quality of life for people with multiple sclerosis, and the burden that their carers experience. The assessment group did not include disutility to carers in its base case because it had questioned whether this was consistent with the NICE reference case. The companies and the Department of Health did include disutilities to carers in their base-case analyses. The base cases in previous NICE technology appraisals for multiple sclerosis (such as [natalizumab](#) and [dimethyl fumarate](#)) also included disutility to carers. The committee concluded that it would include disutility to carers when making its decision.

Health-state costs

The UK MS Survey is the most appropriate source for EDSS health-state costs

3.22 The committee discussed the annual costs associated with each EDSS health state in the model. It noted that the RSS model used Kobelt et al. (2000) in its base case and that this differed from other NICE technology appraisals, which used other sources such as:

- the UK MS Survey used in NICE technology appraisal guidance on [daclizumab](#), [natalizumab](#), [fingolimod](#) and [dimethyl fumarate](#).
- Tyas et al. (2007) used in NICE technology appraisal guidance on [teriflunomide](#) and [alemtuzumab](#).

The committee noted the following about the various sources:

- Kobelt et al. (2000) estimated substantially higher costs in EDSS health states 7–9 than the other sources. Kobelt et al. included indirect costs of sickness absence, early retirement and changes in working hours, which would not be borne by the NHS or personal social services (PSS). Notably, the study did not use recent unit costs, but costs adjusted for inflation from 1999/2000 prices to 15 years later. For these reasons, the committee did not further consider costs from Kobelt et al.
- The UK MS Survey represented the largest data set (responses from 2,048 people), and estimated NHS and PSS costs and costs funded by the UK government. The UK government-funded costs included costs other than what the NHS and PSS would cover, and it was unclear what these included. The committee was satisfied that the NHS and PSS costs estimated from the UK MS Survey were the best available and could be used in this appraisal.
- Tyas et al. (2007) reflected another analysis of data from the UK MS Survey. However, it reported costs funded by the UK government, rather than by the NHS and PSS. Because of this, the committee did not consider costs from Tyas et al. further.

The committee concluded that it would consider only analyses using the UK MS Survey costs for EDSS health states.

Cost of informal care

Costs not covered by the NHS or PSS do not meet the NICE reference case

3.23 Teva stated that the cost of informal care should be considered in this appraisal. [NICE's guide to methods of technology appraisal](#) states that

only 'costs borne by patients may be included when they are reimbursed by the NHS or personal social services' as part of the NICE reference case. The committee noted that, although informal care could be provided by family or carers, it had not been presented with evidence that this informal care would otherwise have been provided by the NHS or PSS. The committee concluded that there was insufficient evidence to include the costs of informal care in the cost-effectiveness analysis.

Cost-effectiveness results

Extavia is a cost-effective use of NHS resources

3.24 The committee considered the cost-effectiveness results for beta interferons and glatiramer acetate, taking into account its preferences, including a waning treatment effect (see section 3.18), using the pooled RSS results (see sections 3.13 and 3.14) and taking into account patient access schemes and discounts with the Commercial Medicines Unit where applicable:

- The incremental cost-effectiveness ratio (ICER) for Extavia compared with best supportive care was below £30,000 per QALY gained. The committee concluded that Extavia was a cost-effective use of NHS resources for people with relapsing–remitting multiple sclerosis or secondary progressive multiple sclerosis with continued relapses.
- The committee considered glatiramer acetate, Avonex, Betaferon, Plegridy, Extavia and Rebif broadly similar in clinical effectiveness (see section 3.9). However, it noted that glatiramer acetate, Avonex, Betaferon, Plegridy and Rebif were more expensive than Extavia. In addition, the ICERs for glatiramer acetate, Avonex, Betaferon, Plegridy and Rebif were all above £30,000 per QALY gained). The committee concluded that glatiramer acetate, Avonex, Betaferon, Plegridy and Rebif were not cost effective at current prices.

Innovation

The technologies are no longer considered innovative

- 3.25 The committee considered that beta interferons and glatiramer acetate may have been considered innovative compared with best supportive care when they became available in the NHS. Several newer technologies are now available that were considered innovative when compared with beta interferons and glatiramer acetate. The committee noted that it had not been presented with any evidence that the additional benefits from innovation with beta interferons and glatiramer acetate were not captured in the cost-effectiveness analysis.

Equality considerations

Special considerations with respect to pregnancy do not apply to glatiramer acetate

- 3.26 Healthcare Improvement Scotland stated that glatiramer acetate is the safest drug to be used in women who want to become pregnant in the future. Although glatiramer acetate is not contraindicated during pregnancy, its marketing authorisation suggests that it is preferable to avoid use during pregnancy. Based on this, the committee concluded that it could not apply special considerations with respect to pregnancy to glatiramer acetate.

4 Implementation

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.

- 4.1 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 determination.

4.2 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 multiple sclerosis and the doctor responsible for their care thinks that Extavia (interferon beta 1b) is the right treatment, it should be available for use, in line with NICE's recommendations.

4.3 The Department of Health and Novartis have agreed that Extavia (interferon beta 1b) will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to **[NICE to add details at time of publication]**

5 Proposed date for review of guidance

5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance along with other treatments for relapsing–remitting multiple sclerosis. NICE welcomes comment on this proposed date. 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 B
December 2017

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.

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.

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.

Thomas Palmer

Technical Lead

Jasdeep Hayre

Technical Adviser

Jeremy Powell

Project Manager

ISBN: **[to be added at publication]**