

**NATIONAL INSTITUTE FOR HEALTH AND CARE  
EXCELLENCE**

**Final appraisal determination**

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

The scope for this technology appraisal includes:

- People with clinically isolated syndrome: NICE is unable to make recommendations for treating clinically isolated syndrome because the diagnostic criteria for multiple sclerosis and clinically isolated syndrome have changed and the treatment pathway has evolved.
- Pegylated interferon beta-1a: NICE is not currently in a position to make recommendations on pegylated interferon beta-1a. There will be a separate single technology appraisal for this drug.

## **1 Recommendations**

1.1 Interferon beta-1a is recommended as an option for treating multiple sclerosis, only if:

- the person has relapsing–remitting multiple sclerosis and
- the companies provide it with the discounts agreed in the patient access schemes.

1.2 Interferon beta-1b (Extavia) is recommended as an option for treating multiple sclerosis, only if:

- the person has relapsing–remitting multiple sclerosis and has had 2 or more relapses within the last 2 years or

- the person has secondary progressive multiple sclerosis with continuing relapses and
- the company provides it with the discount agreed in the patient access scheme.

1.3 Glatiramer acetate is recommended as an option for treating multiple sclerosis, only if:

- the person has relapsing–remitting multiple sclerosis and
- the company provides it with the discount agreed in the patient access scheme.

1.4 Interferon beta-1b (Betaferon) is not recommended within its marketing authorisation as an option for treating multiple sclerosis.

1.5 These recommendations are not intended to affect treatment with a beta interferon or glatiramer acetate 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. For children and young people, this decision should be made jointly by them, their clinician, and their 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 of disability and in reducing the number of multiple sclerosis-related relapses.

The cost-effectiveness estimates for both interferon beta-1b (Extavia) and glatiramer acetate compared with best supportive care are within the range that NICE usually considers a cost-effective use of NHS resources. Extavia needs mixing before it is

injected and some people with multiple sclerosis might find this difficult. Taking this into consideration, interferon beta-1a is also considered an appropriate use of NHS resources even though the range of cost-effectiveness estimates are above what NICE usually considers acceptable. Therefore, interferon beta-1a, interferon beta-1b (Extavia) and glatiramer acetate are recommended as options for treating multiple sclerosis in the NHS.

The most likely cost-effectiveness estimate for interferon beta-1b (Betaferon) is higher than what NICE considers acceptable and it also has to be mixed before use. Therefore, Betaferon is not recommended for multiple sclerosis because it would not be a good use of NHS resources.

The committee is unable to make recommendations specifically for treating clinically isolated syndrome because the diagnostic criteria for multiple sclerosis and clinically isolated syndrome changed in 2010, and the evidence comes from clinical trials done before 2010 and therefore is no longer generalisable to current UK clinical practice.

## **2 Information about the beta interferons and glatiramer acetate**

<p><b>Marketing authorisation indications</b></p>	<p><b>Avonex</b> (interferon beta-1a; Biogen Idec Ltd) 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><b>Rebif</b> (interferon beta-1a; Merck Serono Ltd) 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><b>Betaferon</b> (interferon beta-1b; Bayer Plc) and <b>Extavia</b> (interferon beta-1b; Novartis Pharmaceuticals UK Ltd) 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><b>Copaxone</b> (glatiramer acetate; Teva UK Ltd) is licensed for ‘the treatment of relapsing forms of multiple sclerosis’.</p>
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<p><b>Dosages in the marketing authorisations</b></p>	<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>Betaferon and Extavia are given by subcutaneous injection every other day at a dose of 250 micrograms.</p> <p>Copaxone is given by subcutaneous injection once daily at a dose of 20 mg or 3 times a week at a dose of 40 mg.</p> <p>See the summaries of product characteristics for full dosage schedules.</p>
<p><b>Prices</b></p>	<p>The list price for Avonex is £163.60 per pre-filled pen containing 30 micrograms (excluding VAT, British National Formulary [BNF] online, March 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, March 2017).</p> <p>The list price for Betaferon and Extavia is £39.78 per vial containing 300 micrograms (excluding VAT, BNF online, March 2017).</p> <p>The list price for Copaxone is £18.36 per pre-filled syringe containing 20 mg or £42.83 per pre-filled syringe containing 40 mg (excluding VAT, BNF online, March 2017).</p> <p>Costs may vary in different settings because of negotiated procurement discounts.</p> <p>Four companies have agreed patient access schemes with the Department of Health and Social Care. The levels of the discount are commercial in confidence. These schemes provide a simple discount to the list prices of Avonex, Copaxone, Extavia and Rebif, with the discounts applied at the point of purchase or invoice. The Department of Health and Social Care considered that these patient access schemes do not constitute an excessive administrative burden on the NHS.</p>

### 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 concluded 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 and if they were more effective than anticipated, an increase in price would be permitted. 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 Extavia, but noted that it 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](#), [dimethyl fumarate](#), [fingolimod](#), [natalizumab](#) and [teriflunomide](#). The specific subgroup and line of therapy recommended for each treatment is defined in each appraisal. 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 for people with this complex disease, and most try 1 or more of the beta interferons and 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 most people have treatment until they can no longer walk, when they stop treatment. The committee also understood from the responses to the appraisal consultation document that the frequency of treatment administration may have an effect on adherence to, and therefore the effectiveness of, treatment.

### ***Clinical effectiveness in clinically isolated syndrome***

#### **Clinically isolated syndrome is less relevant than it once was**

3.4 A single demyelinating event is known as clinically isolated syndrome, and people experiencing this have a higher chance of developing multiple sclerosis than people who have never had such an event. The clinical experts present at the third committee meeting stated that the diagnostic criteria for multiple sclerosis changed in 2010. The committee was aware that updated diagnostic criteria published in 2017 did not affect the definition of clinically isolated syndrome. Clinically isolated syndrome is less relevant than 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, and the updated diagnostic criteria also allows using cerebrospinal fluid in the early diagnoses of multiple sclerosis. The committee agreed that the treatment pathway for clinically isolated syndrome had evolved.

**There is insufficient evidence to make any recommendations for clinically isolated syndrome**

3.5 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 assessment group conducted a network meta-analysis for clinically isolated syndrome, which included 5 trials. These used outcome measures based on pre-2010 diagnostic criteria. The committee agreed that all the treatments delayed time to clinically definite multiple sclerosis compared with placebo as it was defined before 2010. However, the committee understood that many patients in the trials would have been diagnosed and treated for multiple sclerosis rather than clinically isolated syndrome if current diagnostic criteria were used instead. Therefore, the committee was concerned that clinical trials using the pre-2010 diagnostic criteria for clinically isolated syndrome were no longer relevant to current UK practice. The committee agreed that a post-hoc analysis which re-identified patients using the 2010 diagnostic criteria showed encouraging results. However, it was concerned that this was based on a single study and had not been validated by any subsequent trials. The committee concluded that there was insufficient evidence using the current diagnostic criteria to make any recommendations for treating clinically isolated syndrome.

## ***Clinical effectiveness in relapsing–remitting multiple sclerosis***

### **Evidence comes from clinical trials and the RSS**

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

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

In addition to the data from clinical trials, the committee also considered data collected from patients participating in the RSS.

### ***Clinical trials***

#### **The trials are broadly generalisable but subject to bias**

3.7 The committee considered the generalisability of the clinical trials to patients in the NHS. The assessment group stated that the trials involving people with relapsing–remitting multiple sclerosis had limitations including differences in design and short length of follow-up. This meant they were at risk of bias because injection-site reactions could have meant that patients in the trials were not blinded to their treatment. The clinical experts stated that unblinding was unlikely to have biased 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 is preferable**

3.8 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 is preferable**

3.9 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 3.10). 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 are similarly effective in reducing the number of relapses and slowing disability progression compared with placebo**

3.10 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. Comparisons between treatments showed differences in the frequency of specific adverse events. However, there was no evidence to suggest that the risk of stopping treatment because of adverse events at 24 months was different between treatments. The committee concluded that all the drugs would cause some adverse effects.

- Quality of life:** The committee was aware that the systematic review informing the network meta-analysis found little evidence comparing the quality-of-life benefits to patients between treatments. It understood that it was not possible to do a network meta-analysis. The committee concluded that, while all treatments were likely to improve quality of life, the difference between treatments was uncertain.

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

Drug	ARR RR (95% CI) <sup>a</sup>	TTP3 HR (95% CI)	TTP6 HR (95% CI)	AEs RiR (95% CI)
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) <sup>b</sup>	0.68 (0.49, 0.94)	1.61 (0.52, 5.02)

All drugs were compared with placebo.  
<sup>a</sup> Results from outlier trial (Bornstein et al., 1987) were excluded.  
<sup>b</sup> Upper 95% confidence interval does not cross 1.00.  
 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**

3.11 The committee discussed the RSS, which included NHS patients treated with either a beta interferon or glatiramer acetate. A representative from

the RSS stated that the scheme included a large number of people and ran for 10 years. 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**

3.12 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 British Columbia 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 for people in the RSS when compared with that expected for people in the British Columbia Multiple Sclerosis cohort on supportive care.

### All treatments in the RSS slowed disease progression

3.13 The implied hazard ratio pooling all treatments in the RSS (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). Companies have indicated that the hazard ratios for individual drugs are confidential, but that all the drugs delayed disease progression similarly compared with best supportive care. The committee concluded that, consistent with the data from trials considered in the assessment group's network meta-analysis, all the technologies offered in the RSS delayed disease progression compared with best supportive care.

### Pooled RSS estimates are preferable

3.14 The assessment group used the pooled effectiveness estimates from the RSS 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 of trials did not show that any particular beta interferon or glatiramer acetate was better than another (see section 3.10).
- 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 choice, and also the outcomes, may have been affected by differences in the patient characteristics. The committee noted evidence provided by Teva in response to the appraisal consultation document that there was a difference between the baseline characteristics of patients having glatiramer acetate and those having beta interferons. It concluded that it had seen no evidence to suggest that these differences were clinically significant.
- 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 also noted an analysis provided by Teva in response to the appraisal consultation document, which used the individual implied hazard ratio for glatiramer acetate and included all patients who switched treatments. It noted that, because similar data from other companies were unavailable, no conclusions could be drawn.

Based on the above considerations, 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**

3.15 Extavia was not included in the RSS because it was licensed after the scheme started. The committee understood that Extavia is 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.

## ***Waning of treatment efficacy***

### **Efficacy does not remain constant over time**

3.16 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.

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## ***Cost effectiveness in relapsing–remitting multiple sclerosis***

### **Versions of the RSS model come from 5 sources**

3.17 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 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 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 changed the assumptions about mortality in the RSS model to avoid double-counting of multiple sclerosis-related mortality (see section 3.20).
- The assessment group excluded treatment costs in EDSS states 7 to 9 (see section 3.26).

### ***Natural history of the disease in subgroup analyses***

#### **The RSS used the British Columbia cohort as a comparator**

3.18 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, in contrast to the British Columbia database, this did not include the possibility that patients' EDSS scores could improve. The committee noted that including the possibility that EDSS scores could improve was appropriate because 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, with data collection having begun in 1980, and that supportive care may have since changed. However, it was also aware that the alternative dataset, from 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 waning of effectiveness over time differs from previous appraisals**

3.19 The assessment group, the 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, but noted the uncertainties about extrapolating over a lifetime. It also noted that the RSS had a follow-up period of 10 years and that no treatment waning assumption was needed for this period because it was captured within the treatment effectiveness data. In addition, it noted that, to extrapolate the waning effect over the treatment lifetime, the RSS model applied a 50% reduction in effect after 10 years. NICE's previous technology appraisals (such as [alemtuzumab](#) and [dimethyl fumarate](#)) 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 because the RSS provided longer follow-up data than the trials in the previous appraisals. It noted that the same reduction in waning effect was applied at the end of the 10-year follow-up period as in the previous appraisals. The committee concluded that assuming a 50% reduction in effect after 10 years was appropriate.

## ***Mortality***

### **The assessment group modified the RSS model to avoid double-counting of mortality**

3.20 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.

**The standardised mortality ratios in Pokorski et al. (1997) overestimate mortality risk in patients with multiple sclerosis**

3.21 An alternative approach to modelling mortality was suggested by Merck Serono, which was based on an assumption that had been used in several previous NICE appraisals ([alemtuzumab](#), [fingolimod](#) and [teriflunomide](#)). This approach applied mortality ratios from Pokorski et al. to each EDSS health state, which resulted in a greater risk of mortality in people with multiple sclerosis than modelled in both the original RSS approach and the assessment group's approach. The committee was concerned that this overestimated mortality, particularly for lower EDSS states, because it was based on outdated data from a period before there had been improvements in multiple sclerosis care and when the background mortality rate was higher. It was also concerned that, in the Pokorski et al. study, EDSS was measured only at the first clinical visit but that the actual EDSS score at time of death depended on the speed of EDSS progression. The committee agreed that the approach using the mortality ratios from Pokorski et al. had limitations and overestimated mortality.

**The standardised mortality ratio reported in Jick et al. (2014) overestimates mortality risk in low EDSS states and underestimates it in high EDSS states**

3.22 The committee considered an alternative approach based on a more recent study (Jick et al., 2014), which reported lower rates of mortality for multiple sclerosis compared with Pokorski et al. (1997) and which had been applied in a recent appraisal for [cladribine](#). The committee understood that although these data were more recent, the publication did not provide separate mortality ratios for different EDSS states. Therefore, models based on Jick et al. apply the same mortality ratio for each EDSS state. The committee was concerned that this approach resulted in clinically implausible mortality rates in low EDSS states and

underestimated mortality in high EDSS states. The committee concluded that the approach to mortality was a source of uncertainty, but accepted the approach taken by the assessment group because it was the most clinically plausible.

### ***Treatment stopping rates***

#### **Rates of stopping treatment from the RSS are appropriate to use in the economic model**

3.23 In its model, the assessment group included rates of stopping treatment 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](#) (the guidance has been withdrawn because the marketing authorisation for daclizumab has been withdrawn) 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). In addition, it understood from the Department of Health that higher stopping rates implausibly improved the cost effectiveness of treatments. The committee concluded that, for this appraisal, it was appropriate to use the same stopping rate from the RSS for all treatments.

### ***Utility values***

#### **Disutility to carers should be considered**

3.24 The committee discussed the quality of life for people with relapsing–remitting 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 [dimethyl fumarate](#) and [natalizumab](#)) 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**

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

The committee noted the following about the various sources:

- Kobelt et al. estimated substantially higher costs in EDSS health states 7 to 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 included separate estimates of costs funded by the UK government and costs funded by the NHS and PSS. 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. reflected another analysis of data from the UK MS Survey. However, it reported costs funded by the UK government only, and did not separately consider costs funded 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 analyses using the UK MS Survey costs for EDSS health states.

### ***Treatment costs***

#### **Treatment costs should not be applied to EDSS states 7 to 9**

3.26 Teva stated that treatment costs should not be applied to EDSS states 7 to 9 because it is unlikely that these people would have treatment with glatiramer acetate or the beta interferons in clinical practice. The assessment group explained that, while many people do not stop treatment at advanced EDSS states, removing treatment costs at EDSS states 7 to 9 reflected a pathway using the drugs within their licensed indications. The committee concluded that it would base its conclusions on analyses without treatment costs applied to EDSS states 7 to 9.

### ***Cost of informal care***

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

3.27 Teva stated that the committee should consider the cost of informal care 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 family or carers may provide informal care, it had not been presented with evidence that the NHS or PSS would otherwise provide this informal care. It agreed that there was insufficient evidence to include the costs of informal care in the cost-effectiveness analysis. The committee also noted consultation

comments from Merck that the committee should consider the additional support provided to patients by companies through schemes such as patient support programmes, and nursing support and training. The committee concluded that this support would be implicitly reflected in the price of the treatments and their benefits, and did not consider it further.

### ***Equality considerations***

#### **Stakeholders consider glatiramer acetate to be the safest drug for anyone who is planning to become pregnant**

3.28 Healthcare Improvement Scotland and several stakeholders during consultation stated that glatiramer acetate is the safest drug for anyone who wants to become pregnant. Although glatiramer acetate is not contraindicated during pregnancy, its marketing authorisation suggests that it is preferable to avoid its use during pregnancy. The committee understood from consultation comments that glatiramer acetate is considered the safest drug available during the pre-conception period.

#### **Special considerations should be given to people who cannot prepare beta interferon-1b treatments**

3.29 The committee noted comments from consultation before the fourth committee meeting that interferon beta-1b is supplied as a solvent and powder, which patients (or carers) must mix each time they administer the treatment. This process is more difficult than treatments employing ready-to-use injection devices. The committee understood that some people will therefore have difficulty using Extavia and Betaferon, particularly people with manual dexterity, visual or cognitive difficulties, which are common in people with multiple sclerosis. The committee concluded that consideration should be given to this group of people with respect to the ease of preparation and administration of beta interferons.



## ***Innovation***

### **The technologies were innovative compared with best supportive care when they became available on the NHS**

3.30 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 have since become available that were considered innovative when compared with beta interferons and glatiramer acetate. The committee noted that the benefits of ease of preparation and administration using auto-injection devices (see section 3.29) were not captured in the cost-effectiveness analysis and took this into account.

## ***Cost-effectiveness results***

### **Interferon beta-1a, interferon beta-1b (Extavia) and glatiramer acetate are a cost-effective use of NHS resources**

3.31 The committee considered the cost-effectiveness results for beta interferons and glatiramer acetate, taking into account its preferences, including waning in treatment effect (see section 3.19), using the pooled RSS results (see sections 3.14 and 3.15) and the patient access schemes where applicable. Specific incremental cost-effectiveness ratio (ICER) values cannot be reported as this would allow the back-calculation of confidential discounts.

- The ICER for interferon beta-1b (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 noted that the ICERs for interferon beta-1a compared with best supportive care were above £30,000 per QALY gained. It took into account the equality considerations applied with respect to the

group of people who will find the preparation and administration of Extavia challenging (see section 3.29) because it was the only beta interferon that was cost effective at a threshold of less than £30,000 per QALY gained. The committee agreed that alternative beta interferons should be available for patients. The committee concluded that interferon beta-1a was a cost-effective use of NHS resources for people with relapsing–remitting multiple sclerosis in this context.

- The ICER for glatiramer acetate compared with best supportive care was below £30,000 per QALY gained. The committee was aware that a generic version of glatiramer acetate is available in the NHS, and understood that the price of glatiramer acetate is likely to fall in the future. The committee concluded that glatiramer acetate was a cost-effective use of NHS resources for people with relapsing–remitting multiple sclerosis.
- The committee considered glatiramer acetate, interferon beta-1a and interferon beta-1b to be broadly similar in clinical effectiveness (see section 3.10). However, it noted that (interferon beta-1b) Betaferon was the most expensive technology. In addition, the ICER for Betaferon was above £30,000 per QALY gained. The committee concluded that Betaferon was not a cost-effective use of NHS resources for people with relapsing–remitting multiple sclerosis.

## 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 determination.

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 multiple sclerosis and the doctor responsible for their care thinks that interferon beta-1a, interferon beta-1b (Extavia) or glatiramer acetate are the right treatment, they should be available for use, in line with NICE's recommendations.

4.4 The Department of Health and Social Care and the companies have agreed that interferon beta-1a (Avonex and Rebif), interferon beta-1b (Extavia) and glatiramer acetate (Copaxone) will be available to the NHS with patient access schemes which make them available with a discount. The size of the discounts are commercial in confidence. It is the responsibility of the companies to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access schemes should be directed to [NICE to add details at time of publication].

## **5 Review of guidance**

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

Amanda Adler  
Chair, Appraisal Committee B  
April 2018

## **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, Alan Lamb**

Technical Leads

#### **Jasdeep Hayre**

Technical Adviser

#### **Jeremy Powell**

Project Manager

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