NICE National Institute for Health and Care Excellence

NICE guidance

Natalizumab (originator and biosimilar) for treating highly active relapsing–remitting multiple sclerosis after disease-modifying therapy

Technology appraisal guidance
Published: 28 January 2026

www.nice.org.uk/guidance/ta1126

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

Natalizumab (subcutaneous originator and intravenous biosimilar)

1.1 Natalizumab (subcutaneous originator or intravenous biosimilar) can be used as an option to treat highly active relapsing–remitting multiple sclerosis (RRMS) in adults, only if:

- it has not responded to a full and adequate course of at least 1 disease-modifying therapy
- the characteristics of the person and the activity of their MS mean that cladribine is not suitable.

  Natalizumab (subcutaneous originator or intravenous biosimilar) can only be used if the companies have an agreed price within the Medicines Procurement and Supply Chain.

1.2 Offer people having natalizumab regular anti-John Cunningham human polyomavirus (JCV) antibody level tests before and during treatment. Use the test specific to the brand being used when starting, or switching to, natalizumab (originator or biosimilar).

Natalizumab (intravenous originator)

1.3 Natalizumab (intravenous originator) should not be used to treat highly active RRMS that has not responded to a full and adequate course of at least 1 disease-modifying therapy in adults.

About these recommendations

1.4 These recommendations are not intended to affect treatment with natalizumab 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 healthcare professional consider it appropriate to stop.

NICE has recommended natalizumab (originator or biosimilar) for rapidly evolving severe RRMS in NICE's technology appraisal guidance on natalizumab for the treatment of adults with highly active RRMS (TA127).

What this means in practice

Natalizumab (subcutaneous originator or intravenous biosimilar)

Natalizumab (subcutaneous originator and intravenous biosimilar) must be funded in the NHS in England for the condition and population in the recommendations, if it is considered the most suitable treatment option.

Natalizumab (subcutaneous originator and intravenous biosimilar) must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that natalizumab (subcutaneous originator and intravenous biosimilar) provides benefits and value for money, so it can be used routinely across the NHS in this population.

NICE has produced tools and resources to support the implementation of this guidance.

Natalizumab (intravenous originator)

Natalizumab (intravenous originator) is not required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendations.

This is because the available evidence does not suggest that natalizumab (intravenous originator) is value for money in this population.

Why the committee made these recommendations

Usual treatment for highly active RRMS after at least 1 disease-modifying therapy includes ocrelizumab, ofatumumab, ublituximab or cladribine.

Clinical trial evidence shows that natalizumab (originator) reduces the rate of relapse compared with placebo. Natalizumab (biosimilar) is expected to work as well as, and be as safe as, natalizumab (originator). Natalizumab (either originator or biosimilar) has not been directly compared in a clinical trial with ocrelizumab, ofatumumab, ublituximab or cladribine. The results of an indirect comparison are uncertain but suggest that natalizumab is likely to work as well as these treatments.

The most likely cost-effectiveness estimates for natalizumab (subcutaneous originator and intravenous biosimilar) when the characteristics of the person and the activity of their MS mean that cladribine is not suitable are within the range that NICE considers an acceptable use of NHS resources. So, natalizumab (subcutaneous originator and intravenous biosimilar) can be used.

The most likely cost-effectiveness estimates for natalizumab (intravenous originator) when the characteristics of the person and the activity of their MS mean that cladribine is not suitable are higher than the range that NICE considers an acceptable use of NHS resources. So, natalizumab (intravenous originator) should not be used.

2 Information about natalizumab (originator and biosimilar)

Marketing authorisation indication

2.1 Natalizumab originator (Tysabri, Biogen) and natalizumab biosimilar (Tyruko, Sandoz) are indicated as a 'single disease-modifying therapy in adults with highly active relapsing–remitting multiple sclerosis (RRMS) for the following patient groups:

- Patients with highly active disease despite a full and adequate course of treatment with at least one disease-modifying therapy (DMT)
  or
- Patients with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesion on brain Magnetic Resonance Imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.'

Dosage in the marketing authorisation

2.2 The dosage schedule for natalizumab originator (subcutaneous and intravenous) is available in the summary of product characteristics for natalizumab originator.

2.3 The dosage schedule for natalizumab biosimilar (intravenous) is available in the summary of product characteristics for natalizumab biosimilar.

Price

2.4 The list prices for the natalizumab originators are:

- £1,130 per 300 mg/15 ml concentrate for solution for intravenous infusion

vials (excluding VAT; BNF online, accessed February 2025).

- £1,130 per 2x150 mg syringe for subcutaneous injection (company submission).

2.5 The list price for the intravenous natalizumab biosimilar is £1,017 per 300 mg/15 ml concentrate for solution for infusion vials (excluding VAT; BNF online, accessed February 2025).

2.6 The companies that make the natalizumab originator and the natalizumab biosimilar have agreed a nationally available price reduction for natalizumab with the Medicines Procurement and Supply Chain. The prices agreed through the framework are commercial in confidence.

Sustainability

2.7 For information, the Carbon Reduction Plans for UK carbon emissions are published on Biogen's webpage on responsibility and Sandoz's website.

3 Committee discussion

The evaluation committee considered evidence submitted by Biogen and Sandoz, an assessment report by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition

3.1 Multiple sclerosis (MS) is a chronic, lifelong condition for which there is no cure. It causes progressive, irreversible disability, and has many symptoms including pain, chronic fatigue, unsteady gait, muscle loss, speech problems, incontinence, visual disturbance and cognitive impairment. Most people have the relapsing–remitting (RR) form of MS, which is characterised by periods of new or worsened symptoms. There are different types of RRMS: active, highly active and rapidly evolving severe forms. Over time, RRMS will progress to secondary progressive MS for many people, which is characterised by progressive disability. For this evaluation, the committee evaluated natalizumab (originator and biosimilar) only for people with highly active RRMS. This is because NICE's technology appraisal guidance for the treatment of adults with highly active RRMS already recommends natalizumab (originator) for people with rapidly evolving severe RRMS but not for people with highly active RRMS. NICE's position statement on biosimilar technologies states that approval for an originator automatically applies to future biosimilars. So, for rapidly evolving severe RRMS, natalizumab (biosimilar) is also recommended.

The clinical experts explained there is variation in the definition of highly active RRMS within the clinical community. The committee noted that the marketing authorisation for natalizumab includes people with highly active disease despite a full and adequate course of treatment with at least 1 disease-modifying therapy. It thought that this was an appropriate definition of highly active disease for the purpose of this evaluation. Patient organisation submissions highlighted that relapses have a significant impact on quality of life and cause painful, debilitating symptoms that make daily activities challenging. The progressive and

unpredictable nature of RRMS can also be emotionally challenging for people with the condition and their carers. The patient expert explained that many people feel a loss of independence when diagnosed with an incurable condition such as MS. As the condition progresses, people become increasingly disabled, which can worsen their quality of life and that of their carers. The committee concluded that RRMS can have a substantial impact on quality of life.

Clinical management

3.2 In the NHS, disease-modifying therapies are used to treat RRMS. The aim of treatment is to reduce the number of relapses, slow the progression of disability, and maintain or improve quality of life. The choice of therapy partly depends on the number of relapses and evidence of disease activity, as defined in each treatment's marketing authorisation. The clinical experts explained that NHS England's treatment algorithm for MS disease-modifying therapies informs prescribing decisions. When a treatment is found to be ineffective for someone, or relapse or disease progression occurs, they may switch to an alternative treatment. Non-pharmacological treatments, such as physiotherapy, are also used to manage the symptoms. The clinical experts explained that, unlike many of the current treatments for highly active RRMS, natalizumab is considered safe to use in pregnancy or when pregnancy is planned. The patient expert highlighted that people with MS find it empowering to have multiple treatment options that control relapses, while still allowing them to do normal daily activities and plan a pregnancy. The committee also noted that natalizumab (originator) is available in an intravenous and subcutaneous form. This could be beneficial for some people, particularly people with poor venous access. The committee concluded that natalizumab would be a welcome additional treatment option for people with highly active RRMS. It noted that natalizumab may be particularly useful in pregnancy or when pregnancy is planned.

Comparators

3.3 The final NICE scope decision problem included beta interferons 1a and 1b, glatiramer acetate, cladribine, fingolimod, ponesimod, ocrelizumab, ofatumumab, alemtuzumab and autologous haematopoietic stem cell transplantation (AHSCT)

as relevant comparators. NHS England's treatment algorithm for MS disease-modifying therapies includes cladribine, fingolimod, ponesimod, ocrelizumab, ofatumumab, alemtuzumab and AHSCT as treatment options for highly active RRMS. At the first committee meeting:

- The companies that make natalizumab (originator and biosimilar) said that natalizumab was likely to be used in people who would otherwise have 'high-efficacy' disease-modifying therapies, that is, ocrelizumab and ofatumumab. The clinical experts agreed that most people would have ocrelizumab and ofatumumab. The committee concluded that ocrelizumab and ofatumumab were relevant comparators.
- The companies noted that alemtuzumab is also considered a high-efficacy disease-modifying therapy but, because it is associated with safety concerns, it is rarely used in the highly active RRMS population. The clinical experts supported this, saying that in clinical practice alemtuzumab is only used in a small proportion of people with very active MS. So, the committee concluded that alemtuzumab was not a relevant comparator.
- Glatiramer acetate and interferon beta 1a and 1b are not listed as options for highly active RRMS after first line in NHS England's treatment algorithm for MS disease-modifying therapies. The clinical experts explained that lower-efficacy treatments such as interferons, glatiramer acetate, fingolimod and ponesimod are not commonly used in highly active RRMS. So, the committee concluded that these treatments were not relevant comparators.
- The company that makes natalizumab (originator) said that AHSCT is used after disease-modifying therapies, so would not be used in people having natalizumab. The professional organisation submission stated that most people would choose not to have AHSCT at this point in the treatment pathway. So, the committee concluded that AHSCT was not a relevant comparator.
- Subcutaneous ocrelizumab has recently been licensed. The clinical experts explained that this would be used interchangeably with the intravenous form in clinical practice. So, the committee concluded that both subcutaneous and intravenous ocrelizumab were relevant comparators.
- NICE's technology appraisal guidance on ublituximab for treating relapsing

MS recommended it at the same position in the pathway as ocrelizumab and ofatumumab. The clinical experts said that ublituximab would be used for highly active RRMS in clinical practice and expected it to be added to the NHS treatment algorithm for MS disease-modifying therapies. So, the committee concluded that ublituximab was a relevant comparator.

The clinical experts noted that some people would have cladribine, but that use of ocrelizumab and ofatumumab is more common. At consultation, the company that makes natalizumab (biosimilar) stated that cladribine is rarely used in the NHS. They noted that it is unsafe to use in pregnancy and while breast feeding, and is less effective than other available high-efficacy treatments. The clinical experts at the second meeting supported this. They explained that, because natalizumab works quickly, it would mainly be used in people with very active RRMS who would otherwise have ocrelizumab or ofatumumab. These people are unlikely to be offered cladribine because it is generally not used when there is a high risk of further relapses, such as in people with a large lesion load or enhancing lesions on imaging. This is to avoid significant disability accrual during treatment with a less effective therapy in this population.

The committee also noted that cladribine is an oral tablet, used as 2-weekly treatment courses over 2 years. This is unlike the other treatments available for highly active RRMS, which are used at set frequencies until disease progression. The committee agreed that, in theory, cladribine was a relevant comparator for natalizumab. But it noted that cladribine is not classed as a high-efficacy treatment. So, it thought that people with highly active RRMS who choose to have cladribine likely do so for the convenience of the treatment. It thought that these people would be unlikely to want continuous treatment with natalizumab. So, the committee thought that there is a distinct population with highly active RRMS having cladribine. But this population is likely small and would generally not have natalizumab. The committee also recalled that natalizumab is safe to use in pregnancy or when pregnancy is planned (see section 3.2). It noted that:

- there are safety concerns associated with use in pregnancy for other MS disease-modifying therapies
- pregnancy must be avoided during the 2-year treatment period with

cladribine and for 6 months after the last dose, and cladribine must be stopped immediately if pregnant

- ocrelizumab, ofatumumab and ublituximab can only be used during pregnancy if potential benefits to the woman, trans man or non-binary person who is pregnant outweighs the risk to the foetus.

The committee concluded that the relevant comparators for natalizumab are ocrelizumab (subcutaneous and intravenous), ofatumumab, ublituximab and cladribine.

Clinical effectiveness

Data sources for natalizumab (originator and biosimilar)

3.4 The main clinical evidence for natalizumab came from the following randomised controlled trials (RCTs) in people with RRMS:

- AFFIRM compared 300 mg of natalizumab originator with placebo in 943 adults over 2 years.
- Saida et al. (2017) compared 300 mg of natalizumab (originator) with placebo in 94 adults over 24 weeks.
- REVEAL compared natalizumab (originator) with fingolimod in 111 people over 52 weeks.
- ANTELOPE compared 300 mg of natalizumab (originator and biosimilar) in 265 adults over 11 months.

The main outcomes assessed were annualised relapse rate (ARR), MRI outcomes and safety data. AFFIRM also included confirmed disability progression (CDP) at 3 and 6 months. The results suggested that natalizumab (originator) improves disease control compared with placebo and fingolimod. There were no RCTs comparing natalizumab with its relevant comparators in the highly active RRMS population (see section 3.3). The effectiveness of natalizumab has also been investigated in non-randomised

studies. TOP, an observational study in 6,321 people with RRMS (134 of whom were in the UK) showed a 90% reduction in ARR compared with the year before starting natalizumab. A post-hoc analysis found similar results in the highly active RRMS population. The EAG noted that this data was helpful to support the randomised data for natalizumab, but highlighted that it did not provide a comparison with other interventions. The committee concluded that natalizumab improves disease control in people with highly active RRMS compared with no treatment.

Progressive multifocal leukoencephalopathy

3.5 The committee noted that several disease-modifying therapies used in highly active RRMS, including natalizumab, are associated with an increased risk of progressive multifocal leukoencephalopathy (PML). PML is a potentially fatal side effect causing white-matter inflammation in the brain, caused by John Cunningham human polyomavirus (JCV). There were no instances of PML reported in the key RCTs for natalizumab, but PML occurred in 53 people having natalizumab (1%) in TOP. The summaries of product characteristics for natalizumab (see sections 2.2 and 2.3) note that the following risk factors are associated with an increased risk of PML:

- presence of anti-JCV antibodies
- treatment duration, especially beyond 2 years
- immunosuppressant use before having natalizumab.

The patient expert explained that the risk of PML is a significant concern and an important factor in the decision to have natalizumab. The clinical experts explained that anti-JCV antibody level tests are mandatory for people considering treatment with natalizumab (originator or biosimilar) to understand the risk of developing PML. Monitoring the risk of PML while on treatment, including 6-monthly tests and frequent imaging, is routine clinical practice. But the clinical experts explained that some people may choose not to have natalizumab because of the risk of PML. The committee also noted that there are separate tests available for natalizumab (originator and biosimilar) that exhibit different sensitivity and specificity, so categorise the

risk of developing PML differently. It agreed that people who are starting, or switching to, natalizumab (originator or biosimilar) should use the test specific to that brand. The committee concluded that people should understand the risk of developing PML before starting natalizumab. They should have regular anti-JCV antibody level tests before and during treatment with the test specific to the brand they are using.

Overview of the network meta-analysis

3.6 The EAG did a systematic review to identify clinical evidence for natalizumab (originator and biosimilar) and the comparators. The EAG's network meta-analysis (NMA) included RCTs in which at least 90% of people had any form of RRMS. The treatments included in the NMA were natalizumab (originator and biosimilar), alemtuzumab, ocrelizumab, cladribine, fingolimod, peginterferon beta 1a, interferon beta 1a, interferon beta 1b, glatiramer acetate, teriflunomide and ponesimod. There was also a subgroup analysis in the highly active RRMS population. The EAG included 42 trials in the full RRMS population, of which 8 included people with highly active disease. The EAG did NMAs for the following key outcomes in people with RRMS: ARR (39 studies included), 3-month CDP (CDP3; 15 studies), 6-month CDP (CDP6; 11 studies), serious adverse events (30 studies) and stopping treatment (29 studies). The results were as follows:

- All MS treatments reduced the rate of all outcomes compared with placebo.
- Alemtuzumab, ocrelizumab and natalizumab (originator and biosimilar) had the greatest improvements for most outcomes, except CDP6, where interferon beta 1b was most effective.
- There was no difference identified in the prevalence of serious adverse events for any of the 14 treatments included in the network.
- There was no evidence of a difference in outcomes for natalizumab (biosimilar) and natalizumab (originator).

  The limited number of trials reporting data in highly active RRMS meant it was only possible to form a network for ARR (7 studies). But the available results showed similar trends to those in the full population. The company that

makes natalizumab (originator) highlighted that there was heterogeneity in the studies in the EAG's NMA. It noted that the heterogeneity included factors that were prognostic of disease progression, including the type and diagnostic criteria for MS and the age of people in the trial. Also, it was concerned that the INCOMIN trial was included in the EAG's NMA. This was because it had inconsistent CDP3 and CDP6 outcomes and was widely considered an outlier by clinical experts. Both companies noted that teriflunomide had only been included in the NMA when needed to connect the network between comparators. They thought that studies comparing teriflunomide with placebo should be included in the NMA because this would lead to a fully connected network. The company that makes natalizumab (biosimilar) highlighted a published NMA by Samjoo et al. (2023), in which teriflunomide was included. The EAG noted that teriflunomide was not a comparator for this evaluation. It acknowledged that including all teriflunomide trials would better connect the network. But it explained that it had explored this in a scenario and it had had minimal impact on the NMA results. The committee concluded that the EAG's NMA was appropriate for decision making.

Assumption of equal efficacy between natalizumab, ofatumumab and ocrelizumab

3.7 The company that makes natalizumab (biosimilar) highlighted that the results of the NMA by Samjoo et al. (2023) suggested comparable efficacy for ARR and CDP6 for natalizumab, ocrelizumab and ofatumumab (see section 3.6). So, it thought that it was appropriate to assume equivalent efficacy between these treatments and appraise natalizumab (both originator and biosimilar) through a cost-comparison approach. The clinical experts noted that natalizumab has a more rapid onset of action than ocrelizumab and ofatumumab. They thought that natalizumab may have slightly improved efficacy outcomes compared with ocrelizumab and ofatumumab, but that this was very uncertain. At the second meeting, the committee considered a cost comparison with natalizumab, ocrelizumab, ofatumumab and ublituximab provided by the company that makes natalizumab biosimilar. The committee acknowledged that using the cost-comparison approach would address some of the uncertainty in the EAG's NMA

(see section 3.6). But it agreed that uncertainty in the treatment effect should not be considered the same as equivalence. So, it was inappropriate to discard the available clinical-effectiveness evidence for natalizumab and comparators. On consideration, the committee agreed that there was not sufficient evidence confirming equal efficacy for natalizumab, ocrelizumab and ofatumumab to justify discarding the results from the EAG's NMA.

Economic model

EAG's modelling approach

3.8 The EAG developed the economic model for this evaluation. It used a discrete-event simulation (DES) model informed by time-to-event data to capture the natural history of RRMS. Everyone in the model had highly active RRMS at baseline. The events captured in the model in people with highly active RRMS were:

- increase and decrease in Expanded Disability Status Scale (EDSS) score
- progression to secondary progressive MS
- relapse
- serious adverse events
- treatment switching because of adverse events
- death.

People could move to secondary progressive MS at any time, after which the events captured were:

- EDSS score increase
- relapse
- serious adverse events
- death.

Each event was associated with a specific cost and quality-of-life value. Patient demographics, disability status, treatment, total costs and quality of life were updated at each event. Results were aggregated over time to provide a summary experience for the whole modelled cohort. The committee noted that the EAG's approach differed from previous RRMS topics, which used Markov models based on EDSS health states. The EAG explained that its approach was more appropriate than a Markov approach to model RRMS. This was because it captured the aim of MS treatment, which was to reduce relapses and disability progression, not reduce EDSS score or secondary progressive MS status. A DES model also allows treatment sequencing to be modelled, which is challenging within the constraints of a Markov model (see section 3.15). The committee acknowledged that the EAG's model addressed some of the limitations of the Markov models in previous MS topics, particularly because it included treatment sequencing and better reflected the natural history of MS. It concluded that the EAG's DES model was appropriate for decision making and preferred it to models used in previous evaluations.

Treatment effectiveness in the model

3.9 The EAG used real-world evidence from the UK MS Register to inform the disease natural history for highly active RRMS and secondary progressive MS in the model. The EAG then calculated treatment-specific event rates for natalizumab (both originator and biosimilar) and comparators for EDSS score increase (CDP6) and relapse. It did this by applying the relative treatment effects from the NMA of RCTs (see section 3.6) to the MS Register data. Treatment effect was taken from the NMA of the all-RRMS population, rather than the analysis in the highly active subgroup. The committee noted that not all treatments had NMA results for all outcomes in the model. When this was the case, the EAG had assumed equal relative effect for treatments with missing outcomes to other MS treatments in the same class. The committee agreed this was appropriate. The EAG calculated rates of serious adverse events and stopping treatment because of adverse events by applying the relative treatment effects from the NMA to baseline rates from AFFIRM. No treatment-specific event rates were applied for people with secondary progressive MS. The committee recalled that both subcutaneous and

intravenous ocrelizumab were relevant comparators for natalizumab (see section 3.3). But it noted that the EAG's base case only included intravenous ocrelizumab. It acknowledged that the EAG had provided a scenario including subcutaneous ocrelizumab. In this scenario, it assumed equal effectiveness but lower administration costs based on those used in NICE's technology appraisal guidance on ublituximab. The committee noted that this had a limited impact on the cost-effectiveness results. The committee concluded that the EAG's approach to modelling treatment effectiveness for natalizumab and comparators was acceptable for decision making.

Natural history data for RRMS

3.10 The committee noted that previous NICE technology appraisals in RRMS had used the British Columbia Multiple Sclerosis (BCMS) or London Ontario MS databases to inform the natural history of RRMS. It noted that both these databases were Canadian and the data collected was old. The BCMS database collected data between 1975 and 2003 and the London Ontario MS database collected data between 1972 and 1984. So, they did not reflect the outcomes for people with RRMS having current treatment options. The MS Register collected data from people in the UK between 2017 and 2024. But the clinical experts explained that the MS Register data was not fully representative of people with RRMS in NHS clinical practice. This was because the data from the MS Register was self-reported through questionnaires, which is time consuming for people with MS. Because of this, the data overrepresented people who had more time available, including older people and people living in less deprived areas. The EAG acknowledged the limitations in using the MS Register data, in that the sample size was small and the population did not fully match the decision problem. The clinical experts at the first meeting thought that the MSBase Registry may be a more appropriate source of data for people with RRMS. This is an international database that has collected data on people with MS since 2004.

The committee was concerned about the appropriateness of using the BCMS and London Ontario MS databases. This was because, in previous NICE technology appraisals in RRMS that used these databases, people with MS had faster disease progression. Also, a larger proportion of people had more severe EDSS scores than expected in clinical practice. In the EAG's model using the MS

Register data, disease progression was slower than in previous models, and very few people had an EDSS score of 7 and over. The clinical experts said that, in current clinical practice, fewer people have disease progression to the more severe EDSS scores. This is because of better outcomes with current RRMS treatments, earlier diagnosis and improvements in non-pharmacological symptom management. But they noted that the MS Register data is also likely to underrepresent people with more severe disease (such as EDSS scores 8 [full time wheelchair user] and 9 [unable to get out of bed]) who would be less able to complete the questionnaires. This meant that missing data was unlikely to be missing at random.

At consultation, the Multiple Sclerosis Trust commented that the MS Register data may underestimate the number of people with advanced MS (that is, high EDSS states). This is because many people living with advanced MS are cared for outside of secondary care, for example, through their GP or in a residential care home. So, they may not be captured in the MS Register. The clinical experts thought that the average time spent in the EDSS states in the EAG's model was generally reasonable. But they highlighted that the average time spent with an EDSS score of 6 in the EAG's model was short compared with that expected in clinical practice. They highlighted that the Canadian databases were not generalisable to highly active RRMS that had progressed on disease-modifying therapy. This was because they were in an untreated population. The committee acknowledged there may be some issues with missing data and the generalisability of the MS Register data to NHS clinical practice. But they thought that there were also issues with the Canadian databases, particularly that they were old and did not reflect current NHS practice. It noted that the EAG had completed a Data Suitability Assessment Tool (DataSAT) for the MS Register in line with NICE's real-world evidence framework. Also, it noted that it had not been presented with scenarios that used the MSBase, BCMS or London Ontario MS databases for natural history data. The committee concluded that there was uncertainty about the most appropriate data source for natural history of RRMS. But, given the currently available evidence, it agreed that the MS Register was the most recent and relevant data source for natural history data. It also thought that the MS Register captured the gradual progression of highly active RRMS with high-efficacy disease-modifying therapies.

Progression to secondary progressive MS

Rate of progression

3.11 The proportion of people transitioning to secondary progressive MS in the EAG's model was informed by the rates for people with highly active RRMS in the MS Register. In the model at the first meeting, the average time to secondary progressive MS was 9.7 years, and 86% of people progressed to secondary progressive MS over the model lifetime (around 40 years). The clinical experts were concerned that the EAG's model may have overestimated time to secondary progressive MS compared with the UK population. This was because the MS Register overrepresents older people with MS, who are more likely to have progressed to secondary progressive MS.

At consultation, the EAG provided the predicted proportion with secondary progressive MS at 5, 10 and 15 years after entering the EAG's model. The clinical experts thought that these values were implausibly high for the population with highly active RRMS in current NHS clinical practice. They explained that the availability of high-efficacy disease-modifying therapies has considerably reduced the rate of progression to secondary progressive MS in recent years. They thought that the rates of progression to secondary progressive MS seen in the NHS are around half those in the EAG's model. The clinical experts were concerned that people could progress from any EDSS state in highly active RRMS to secondary progressive MS. They noted that a diagnosis of secondary progressive MS needs disability worsening over time. So, in clinical practice, they would not diagnose secondary progressive MS in people with EDSS scores of 4 and under. The committee noted that the proportion of people progressing to secondary progressive MS was likely correlated with the EDSS score for highly active RRMS. But the EAG had identified no robust data to inform this. The committee agreed that the EAG's model likely overestimated the proportion of people with secondary progressive MS.

After the second committee meeting, the EAG updated its model to stop people with RRMS and an EDSS score of 4.5 or under from progressing to secondary progressive MS. This reduced the proportion of people progressing to secondary progressive MS at 5, 10 and 15 years in the model by over half. The committee acknowledged that this was more aligned with clinical advice at the second

meeting. It agreed that, ideally, rates of transition to secondary progressive MS would be modelled as being conditional on the EDSS state of people with highly active RRMS. But it acknowledged that a model with better face validity in this area would be unlikely to produce materially different results. So, given the options presented, it concluded that limiting progression to secondary progressive MS to people with an EDSS score over 4.5 was acceptable for decision making.

Treatment effect on progression rates

3.12 At the first meeting, the committee noted that the rate of progression to secondary progressive MS was assumed to be the same for all treatments in the EAG's model. The EAG highlighted that this approach aligned with clinical expert advice it had received and other NICE technology appraisals in RRMS. The clinical experts highlighted that there was no evidence on the time to secondary progressive MS progression after having specific treatments from clinical trials. They explained that this was because it takes 25 to 30 years for people with RRMS to develop secondary progressive MS. At the second meeting, the clinical experts thought that equal rates of progression to secondary progressive MS for natalizumab and comparators were plausible providing these treatments were working. But they noted that the modelled treatments were known to have different rates of clinical effectiveness, which may have somewhat affected time to progression to secondary progressive MS. It recalled its preference for modelling progression to secondary progressive MS as being conditional on EDSS state in highly active RRMS (see section 3.11). It noted that this approach would indirectly model treatments that slow progression through EDSS states to benefit from a slower time to secondary progressive MS. But the committee acknowledged the challenges in collecting data on treatment effect on progression to secondary progressive MS. It agreed that the impact of disease-modifying therapies on progression to secondary progressive MS was an area of uncertainty, but accepted the EAG's approach for decision making.

Efficacy assumptions for intravenous natalizumab (originator and biosimilar)

3.13 At the first committee meeting, the EAG included intravenous natalizumab (originator and biosimilar) separately in the NMA (see section 3.6). It then modelled intravenous natalizumab (both originator and biosimilar) as separate clinical products in its model, using different efficacy assumptions for each. The company that makes natalizumab (biosimilar) said that this was inappropriate. It highlighted that NICE's position statement on biosimilar technologies states that approval for the originator automatically applies to future biosimilars. Also, clinical trials for biosimilars are small and focused on meeting regulatory requirements. So, the biosimilar is at a disadvantage if it is considered as a separate product. So, the company thought that intravenous natalizumab (originator and biosimilar) should be modelled as equally effective to natalizumab (originator), and that they should differ only in costs. The clinical experts explained that biosimilars are thought to be clinically equivalent and interchangeable with the originator in clinical practice. Based on the committee's preference at the first meeting, the EAG updated its base case after consultation to assume that natalizumab (biosimilar) had equal efficacy to natalizumab (originator), and that they differed only in costs. The committee concluded that it was appropriate to assume that natalizumab (biosimilar) was clinically equivalent to natalizumab (originator).

Stopping and switching treatment

3.14 The EAG's model used stopping treatment because of adverse events as a proxy for stopping treatment and progression to subsequent treatments. The EAG referred to this as treatment waning. At the first committee meeting, the stopping rates because of adverse events from AFFIRM were used for natalizumab (originator) and those from ANTELOPE were used for natalizumab (biosimilar). For comparators, the NMA treatment effects were applied to the AFFIRM baseline rates. The company that makes natalizumab (originator) noted that using stopping treatment because of adverse events as a proxy had been a concern in previous NICE technology appraisals in RRMS. It highlighted that NICE's technology appraisal guidance on cladribine for treating relapsing MS recommended using a broader definition beyond just adverse events. The clinical experts explained that most people stop natalizumab because they become JCV

positive, are concerned about the risk of PML or have an adverse event (see section 3.5). The committee also recalled that natalizumab is thought to be safe to use in pregnancy, unlike other high-efficacy disease-modifying therapies (see section 3.2). The patient expert explained that natalizumab is often used during and immediately after pregnancy, followed by a switch to a disease-modifying therapy with a lower risk of PML for long-term use. So, the clinical experts explained that most people who stop natalizumab would not have stopped because of loss of effect or because of an adverse event.

At consultation, the company for natalizumab (biosimilar) stated that it was inappropriate to model waning of treatment effect because response to disease-modifying therapies was binary. That is, people with MS either have a response to a disease-modifying therapy or have no response, and there is no reduction in treatment effect over time. The clinical experts at the second committee meeting explained that a gradual decrease in benefit would be unlikely with the high-efficacy treatments included in the EAG's model. The EAG confirmed that this reflected the modelling, which assumed no waning of effect for disease-modifying therapies at an individual level. But the committee thought that treatment waning was a population, not an individual, effect that resulted from a gradual increase in the proportion of the modelled population swapping to third-line treatments because of lack of effect. After consultation, the EAG maintained its preference for using the rates of stopping treatment because of adverse events in its base case. But it used the rates from AFFIRM for natalizumab (both originator and biosimilar). It also provided a scenario that assumed 10% of people stop natalizumab and comparators over 5 years (that is, 2% stopping rate per year). This was based on a recent audit by a clinical expert to the EAG. This showed a stable rate of breakthrough activity of 5% to 10% up to 5 years for people having disease-modifying therapies. The clinical experts highlighted that the rate of stopping treatment would not be constant. They highlighted that most people stop natalizumab between 18 and 24 months after starting treatment because the risk of PML increases substantially at this point. They highlighted that 52.2% of people in TOP stopped treatment with natalizumab over a 10-year period (see section 3.4). This also broadly aligned with the proportion of people with anti-JCV antibodies in the NHS. So, the committee agreed that the EAG's scenario likely underestimated the proportion of people who stopped natalizumab. After the second committee meeting, the EAG provided data from the model that showed that 88.0% people that started natalizumab as their first

modelled treatment were still having it after 10 years. Because of this, the committee was concerned that the EAG's model may have underestimated the effect of stopping and switching treatments. It agreed that stopping treatment for adverse events was not a suitable proxy for people stopping or switching treatment in the model and did not reflect the available clinical evidence. But it also noted that the EAG's alternative approach had a limited impact on the cost-effectiveness results. The committee concluded that the proportion stopping and switching treatments was highly uncertain. But, given the analyses available to it, it considered analyses using stopping treatment because of adverse events as a proxy in its decision making.

Subsequent treatments in the model

3.15 The EAG's model included subsequent treatments for people who stopped natalizumab or comparators. At the first committee meeting, this was based on the treatments available at third and fourth line in NHS England's treatment algorithm for MS disease-modifying therapies. The EAG highlighted that 35% of people in the model had third-line treatment (that is, 1 additional subsequent treatment) and 34% of people had fourth-line treatment (a second subsequent treatment) over the modelled lifetime. People who developed secondary progressive MS were assumed to have a basket of siponimod or interferon beta 1b as a weighted average by use in the MS Register. For people who needed further lines of treatment for RRMS, the EAG assumed that there was an equal likelihood of having any available subsequent treatment. The clinical experts noted that people who needed subsequent treatments would usually have ocrelizumab, ofatumumab or ublituximab, but some people may have cladribine. The committee also agreed that previous RRMS treatments were likely to influence the choice of subsequent treatments, so the EAG's model was a simplification.

At consultation, the EAG updated its model to use data on subsequent treatments at third line from the MS Register for ocrelizumab, ofatumumab and cladribine. It also assumed that, once people had a treatment, they could not have it again and that there was an equal chance of having all available therapies from fourth line onwards. The committee recalled that ublituximab had recently been recommended (see section 3.3). It noted that it was not included as a subsequent

treatment because no one in the MS Register had used it at the time of the analyses. The EAG acknowledged this uncertainty and provided scenarios that assumed 100% of people had each of ocrelizumab, ofatumumab or ublituximab at fourth line at consultation. The clinical experts at the second meeting confirmed that the subsequent treatments used in the MS Register at third line aligned with those expected in the NHS. The committee recalled that previous NICE technology appraisals in RRMS had not modelled subsequent treatments for RRMS, which was a substantial limitation in representing the natural history of the condition. The committee thought that the ability of the EAG's model to include subsequent treatments was a considerable improvement on previous RRMS models. It concluded that the EAG's modelling of subsequent treatments after consultation, including using MS Register data for third-line options, was appropriate for decision making.

Stopping treatment at high EDSS scores

3.16 People in the EAG's original model continued treatment regardless of their EDSS score. The company that makes natalizumab (originator) highlighted at consultation that previous RRMS topics have included a rule that people stop treatment once they reach EDSS score 7. This was in line with the Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in MS and NHS England's treatment algorithm for MS disease-modifying therapies. Both of these recommend that treatment in RRMS is stopped once people are unable to walk. The EAG updated its model after consultation on the assessment report to apply a stopping rule at EDSS score 7. The committee agreed that this was appropriate.

Mortality

3.17 At the first committee meeting, the EAG applied a single all-cause excess standard mortality rate (SMR) of 1.68 for people with MS compared with the general public from Jick et al. (2014). So, it assumed that there was no additional mortality associated with higher EDSS scores compared with lower EDSS scores. The EAG also presented scenario analyses using mortality rates that varied by EDSS score. It used data from Sadovnick et al. (1992; reported in Pokorski 1997)

and Harding et al. (2018). Sadovnick et al. reported stratified mortality data, with an SMR of 1.60 for mild (EDSS score 0 to 3), 1.84 for moderate (EDSS score 4 to 6) and 4.44 for severe RRMS (EDSS score 7 to 9), from an analysis by the MS Society of Canada between 1972 and 1985. Harding et al. reported mortality data by more granular EDSS classes with SMRs ranging from 2.02 (EDSS scores 4 to 5.5) to 60.74 (EDSS scores 9 to 9.5). This was based on MS registry data collected in southeast Wales between 1985 and 2015. The clinical experts confirmed that having a higher EDSS score was associated with increased mortality compared with having a lower EDSS score. The committee noted that Harding et al. did not provide data for EDSS scores under 4, so the EAG had used the SMR from Jick et al. for these EDSS scores. But the clinical experts were concerned that the SMR for people with mild-to-moderate disability in Harding et al. was higher than expected in NHS clinical practice. They thought that people with a mild EDSS score would have a mortality rate similar to the general population. The clinical experts were also concerned that the SMRs associated with more severe EDSS health states in Harding et al. were very high. But, because very few people in the EAG's model progressed to EDSS scores of over 7, this was unlikely to have had a large effect on the overall mortality rate. It acknowledged that Harding et al. may have overestimated mortality rates compared with the current population with RRMS in the NHS.

After consultation, the EAG updated the approach to modelling mortality in its base case. In this, it used the SMRs from Harding et al. as an indication of the relative difference between EDSS scores in people with highly active RRMS. But it calibrated the average SMR across all EDSS states to equal that from Jick et al. SMRs were calculated relative to the EDSS 4 state because people spent most of their time in EDSS 4 over the model lifetime. The resulting SMRs ranged from 1.40 (EDSS scores 0 to 3) to 50.52 (EDSS score 9). The clinical experts thought that these were more in line with what is expected in clinical practice. But they were concerned that an SMR of 1.40 for EDSS scores 0 to 3 might over-estimate mortality in these states because these people have few or no symptoms. The EAG had also applied the SMR for EDSS score 7 (3.96) to EDSS scores 8 and 9 in the model to avoid use of extreme mortality rates for these states. The committee queried whether this was appropriate given that people with EDSS states 8 and above are restricted to bed for most of the day. But the clinical experts explained that people with higher EDSS scores are living longer because of improvements in care. The EAG also highlighted a scenario applying the higher

mortality rates for EDSS scores 8 and 9, which had limited effect on the cost-effectiveness results. The committee agreed that the mortality rates for people with highly active RRMS were uncertain and that all the available sources of mortality data had limitations. It noted clinical expert opinion that the EAG's base-case assumption after consultation most aligned with the mortality rates expected in clinical practice. So, the committee thought that applying the average SMR across EDSS levels from Jick et al. with differences between EDSS categories matched to Harding et al. was appropriate for decision making.

Utility values

Source of utility values

3.18 Utilities in the EAG's model were modelled as being specific to EDSS scores for both RRMS and secondary progressive MS. The base-case utilities were from the UK MS Survey 2005 reported by Orme et al. (2007). This was a cross-sectional study of 2,048 people with MS collecting self-reported EQ-5D and resource use. Carer disutilities were also modelled as varying by EDSS score from a survey of 200 carers by Acaster et al. (2011). The committee noted that the EAG's preferred utility sources had been accepted in several previous RRMS topics, including in the committee discussion for NICE's technology appraisal guidance on ponesimod for treating RRMS. The EAG also included disutilities for commonly occurring serious adverse events and a one-off disutility for relapse. The committee agreed that the EAG's utility values were appropriate.

Costs

Natalizumab dosing regimen

3.19 The EAG modelled natalizumab (originator and biosimilar) as a 300 mg dose every 4 weeks in its base case, in line with their relative marketing authorisations. The summaries of product characteristics for natalizumab (both originator and biosimilar; see sections 2.2 and 2.3) report 6-weekly extended interval dosing as

beneficial for people who have anti-JCV antibodies, to lower the risk of PML. For natalizumab (originator), this was for both the subcutaneous and intravenous forms. The company that makes natalizumab (originator) highlighted data from the NOVA phase-3 RCT. This data suggested that people who were having stable intravenous natalizumab (originator) every 4 weeks could switch to 6-weekly dosing with no meaningful loss of efficacy and safety. But the clinical experts noted that the data is less robust for 6-weekly dosing with subcutaneous natalizumab (originator), particularly in pregnancy. The clinical experts said that in their clinical practice around 60% to 70% of people having natalizumab for rapidly evolving severe RRMS currently have 6-weekly dosing. They noted that most people who have anti-JCV antibodies and some people who do not have anti-JCV antibodies have natalizumab every 6 weeks. They explained that 6-weekly dosing is routinely used in pregnancy and when breastfeeding. Some people also choose 6-weekly dosing because they feel unwell with 4-weekly dosing or find it easier to manage existing work and childcare commitments. But some people may have 4-weekly dosing to ensure full treatment effect, particularly people with a high body weight. The committee noted that the risk of developing PML is substantially reduced with 6-weekly dosing. At consultation, the EAG updated its base case to include 6-weekly dosing for 60% of people having natalizumab (originator or biosimilar), regardless of the administration route. The committee concluded that this assumption was appropriate for decision making.

Costs for anti-JCV antibody testing

3.20 The committee recalled that anti-JCV antibody tests are needed before starting natalizumab and every 6 months after that for people whose results are negative at baseline. This is to manage the risk of developing PML (see section 3.5). The companies that make natalizumab (originator and biosimilar) explained that they provide anti-JCV tests free to the NHS. But the EAG included costs for anti-JCV antibody testing in its model for both technologies, based on advice from its clinical experts. Both companies said that this was inappropriate, highlighting that there were no known issues in accessing the relevant tests. The clinical experts at the first committee meeting confirmed that there is no NHS-funded anti-JCV antibody test available. So, the companies' tests are always used in clinical practice. After consultation, the EAG updated its base case to remove all costs

for anti-JCV antibody testing. The committee agreed that the costs of anti-JCV antibody testing should not be in the model for natalizumab (either originator or biosimilar).

Resource use

Natalizumab administration routes

3.21 Natalizumab (originator) is available as intravenous and subcutaneous formulations (see section 3.2). Subcutaneous natalizumab can be administered in secondary care or at home by a healthcare professional. The EAG modelled the different formulations as separate products. The EAG's clinical experts advised that there were no differences in resource use between formulations, so the EAG assumed equal resource use for each in its base case. At the first committee meeting, the company that makes natalizumab (originator) said that subcutaneous natalizumab was associated with reduced administration time and so reduced treatment burden and NHS costs. The clinical experts at the first committee meeting noted that, in secondary care, it is more efficient to administer subcutaneous natalizumab than intravenous natalizumab. But they thought that the overall time saving with subcutaneous natalizumab was minimal.

At consultation, the company that makes natalizumab (originator) highlighted a costing model that estimated considerable savings with subcutaneous natalizumab from reduced consumables. It also estimated increased infusion chair and nursing capacity on switching from intravenous to subcutaneous natalizumab (originator). (The exact results are confidential and cannot be reported here.) The EAG noted that the company's costing model was informative. But it noted that the infusion costs in the model were based on Healthcare Resource Group (HRG) codes, which was aligned with other NICE technology appraisals in RRMS. So, the model did not include staff hours separately. The EAG provided a scenario at consultation that included a 50% reduction in administration costs (but equal monitoring costs) for subcutaneous compared with intravenous natalizumab in the first year of use, after which people switched to home administration (see section 3.22). One clinical expert at the second committee meeting said that the number of people they can treat in a unit daily has doubled since swapping 60% of people from intravenous to

subcutaneous natalizumab (originator) for rapidly evolving severe MS. But they were concerned that the EAG's scenario may have overestimated the cost savings with subcutaneous natalizumab. This was because people still needed to come into hospital and be assessed by an MS nurse before having natalizumab. They also highlighted that use of subcutaneous natalizumab for rapidly evolving severe MS is decreasing in some centres. This is because of patient preference and the availability of a cheaper biosimilar that can only be used intravenously. But the company explained that there is considerable variation in the uptake of subcutaneous natalizumab throughout the NHS.

After the second committee meeting, the EAG updated its model to use a more recent cost code for intravenous administration. The committee agreed that this was appropriate. It concluded that subcutaneous administration would have a reduced administration time compared with intravenous administration. So, it agreed that it was appropriate to model subcutaneous and intravenous natalizumab separately. But it noted that it had not seen robust estimates of the reduction in time included. It concluded that, of the analyses available to it, the most appropriate was to apply a 50% reduction in administration costs for subcutaneous compared with intravenous natalizumab. It considered this during its decision making.

Home administration of subcutaneous natalizumab (originator)

3.22 At the first meeting, the company that makes natalizumab (originator) highlighted that it funds a home administration service by a nurse for the subcutaneous formulation. It was concerned that the cost savings and benefits from home administration had not been included in the EAG's model. The clinical experts said that subcutaneous natalizumab is normally administered in secondary care because of concerns about the continuity of funding for the home administration service. They highlighted that regular clinical contact is also important in mitigating the risk of PML and they were concerned that this would be lost with home administration. For this reason, they agreed that home administration of subcutaneous natalizumab would not be appropriate for people with positive anti-JCV antibody test results. At the second committee meeting, the company that makes natalizumab (originator) noted that, although there is regional variation, uptake of the home administration service is increasing in the NHS, with

some centres keen to use the service. The committee noted that the EAG provided a scenario including home administration (see section 3.21). The scenario assumed that all subcutaneous natalizumab was given at home by a company funded nurse after the first year (that is, these people accrued no administration costs in the model after the first year). The committee noted that this aligned with the summary of product characteristics for natalizumab (originator), which specifies that people need to have 6 injections in hospital before moving to home administration. But the committee thought that it was implausible that everyone having subcutaneous natalizumab would have long-term home administration by a company funded nurse. This was because of additional monitoring for people with positive anti-JCV antibody test results and the perceived risk of withdrawal of the home administration service by some centres. The committee agreed that there would be some reduction in costs for the population having subcutaneous natalizumab from use of the home administration service. It also thought that uptake of the home administration service is likely to differ throughout the NHS. But it thought that the level of uptake and long-term durability of the home administration service was unclear. It preferred not to include home administration in its base case, but thought that the potential benefits of home administration were an uncaptured benefit.

Cost-effectiveness estimates

Net monetary benefit

3.23 Cost effectiveness was assessed by calculating incremental net monetary benefit (NMB) instead of the incremental cost-effectiveness ratio (ICER). This was because the EAG thought that it better captured the uncertainty in the cost-effectiveness estimates. The EAG compared the incremental NMB of subcutaneous and intravenous natalizumab (originator), and intravenous natalizumab (biosimilar), using its preferred assumptions, with other MS treatments. It did this at threshold values of £20,000 and £30,000 per quality-adjusted life year (QALY) gained. The committee noted that the credible intervals in the incremental NMB crossed zero for most of the analyses comparing intravenous and subcutaneous natalizumab (originator) and intravenous natalizumab (biosimilar) with other comparators. This suggested that, at a 95%

credibility level, as well as a positive net benefit, net harm was among the range of possible cost-effectiveness results for natalizumab. But the committee agreed that it could use the EAG's expected results for decision making, while also considering the substantial uncertainty associated with the model outputs.

Uncaptured benefits

3.24 The committee considered whether there were any uncaptured benefits of natalizumab:

- It recalled that natalizumab is safe to use in pregnancy or when pregnancy is planned (see section 3.2). It noted that all other currently available treatments for highly active RRMS have a safety warning for use in pregnancy. It acknowledged that the decision space was different in this population and that natalizumab addressed an unmet need. It agreed this benefit was not captured in the modelling.
- The committee thought that there are potential benefits for subcutaneous natalizumab (originator) that had not been captured in the modelling. These included cost savings from company funded home administration and potential environmental benefits associated with reduced consumables (see section 3.22).

The committee considered these uncaptured benefits in its decision making.

Committee preferred assumptions and analyses

3.25 Based on the available evidence, the committee's preferred assumptions included:

- including ocrelizumab (subcutaneous and intravenous), ofatumumab, cladribine and ublituximab as comparators (see section 3.3)
- using the EAG's base-case NMA to inform efficacy assumptions in the model (see section 3.6)
- using the MS Register data for the time-to-event data for the natural history

of RRMS (see section 3.10)

- limiting progression from highly active RRMS to secondary progressive MS to people with EDSS scores of over 4.5 (see section 3.11)
- assuming that the clinical effectiveness of natalizumab (biosimilar) is the same as for natalizumab (originator; see section 3.11)
- using stopping rates caused by adverse events as a proxy for people stopping and switching treatment in the model while noting the uncertainty in this estimate (see section 3.14)
- using the subsequent treatments from the MS Register for third-line treatments and assuming an equal distribution of available treatments at fourth line onwards (see section 3.15)
- using the average SMRs from Jick et al. (2014) with differences between EDSS categories matched to Harding et al. (2018; see section 3.17)
- including 6-weekly dosing for 60% of people having natalizumab (see section 3.19)
- excluding the costs of anti-JCV antibody testing for natalizumab (both originator and biosimilar; see section 3.20)
- assuming a 50% reduction in administration costs for subcutaneous natalizumab (originator; see section 3.21).
- assuming no use of home administration of subcutaneous natalizumab (originator; see section 3.22).

The committee decided that there was considerable uncertainty around several of its preferred assumptions. These included the administration and monitoring costs for subcutaneous natalizumab (originator), the proportion stopping and switching treatment, and the rate of progression to secondary progressive MS. But it also thought that there were benefits that were not captured in the modelling, especially in pregnancy or when pregnancy is planned, or for people having subcutaneous natalizumab (originator; see section 3.24). Because of this, it agreed that the appropriate threshold was around the middle of the range NICE considers a cost-effective use of NHS

resources (£20,000 to £30,000) per QALY gained. After the second committee meeting, the EAG provided an analysis that included all of the committee's preferred assumptions. The cost-effectiveness results were above the range that NICE considers an acceptable use of NHS resources when including all of its preferred comparators. But the committee recalled that there was a large population who would have natalizumab but not cladribine (see section 3.3). This is because cladribine would not be used in people who wish to conceive in the near future or whose condition is likely to relapse. It also recalled that people who choose cladribine do so because of convenience, so would be unlikely to want regular treatment with natalizumab. Because of this, the committee agreed that it was appropriate to also consider cost-effectiveness results when the characteristics of the person and the activity of their MS mean that cladribine is not suitable. In these analyses, natalizumab (subcutaneous originator and intravenous biosimilar) had a positive incremental NMB, while natalizumab (intravenous originator) had a negative incremental net benefit. This confirmed that natalizumab (subcutaneous originator and intravenous biosimilar) are cost effective compared with ocrelizumab, ofatumumab and ublituximab at £25,000 per QALY gained.

Other factors

Equality

3.26 The committee considered a number of potential equality issues that were raised at scoping and in stakeholder submissions:

- A patient organisation submission highlighted that a higher proportion of people with highly active RRMS are female than male. The committee noted that the issue of sex-related disease prevalence could not be addressed in a NICE technology appraisal.
- The committee noted that the onset of MS may coincide with family planning and recalled that most high-efficacy disease-modifying therapies cannot be used in pregnancy or when pregnancy is planned. Pregnancy and maternity are protected characteristics under the Equality Act 2010. The committee

recalled that natalizumab had proven safety data in pregnancy, so a positive recommendation for natalizumab in highly active RRMS would address this unmet need. The committee thought that this was an uncaptured benefit in its decision making (see section 3.24).

- A professional organisation also stated that currently, people with highly active RRMS have to wait for another, potentially disabling relapse to meet the criteria for rapidly evolving severe RRMS to access natalizumab. The committee noted that this was not an equality issue.
- At scoping, it was raised that because natalizumab has the potential for home administration, a negative recommendation would disproportionately affect people who live far from a treatment centre. This is particularly the case for people for whom travelling is difficult, or who have more limited access to transport. The committee recalled that its recommendation included both subcutaneous and intravenous natalizumab (originator).
- At consultation, a professional organisation highlighted that people with MS who are older often have a higher risk of infections or have comorbidities that complicate management decisions. These people would benefit more from natalizumab's non-immunosuppressive mechanism of action. The committee considered this in its decision making.

The committee considered the equalities issues in its decision making.

Conclusion

Recommendation

3.27 The committee concluded that there were uncertainties in the cost-effectiveness evidence. But, when also considering uncaptured benefits, natalizumab (subcutaneous originator and intravenous biosimilar) were cost-effective treatments when the characteristics of the person and the activity of their MS mean that cladribine is not suitable. But natalizumab (intravenous originator) was not. So, in this population, natalizumab (subcutaneous originator and intravenous biosimilar) can be used but natalizumab (intravenous originator) should not be

used.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 Section 4f of The Innovative Medicines Fund Principles states that a discretionary source of early funding (from the overall Innovative Medicines Fund budget) is available for certain medicines recommended by NICE. In this instance, interim funding has been agreed for natalizumab (subcutaneous originator or intravenous biosimilar). Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.4 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 highly active relapsing–remitting multiple sclerosis and the healthcare professional responsible for their care thinks that natalizumab (subcutaneous originator or intravenous biosimilar) are the right treatments, they should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation 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 being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Baljit Singh
Chair, technology appraisal committee B

NICE project team

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

Emma Douch
Technical lead

Lizzie Walker
Technical adviser

Vonda Murray and Thomas Feist

Project managers

Richard Diaz
Associate director

ISBN: 978-1-4731-8645-3