NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using natalizumab in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

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

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

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

Issue date: March 2025

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

After consultation:

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using natalizumab in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 2 April 2025
- Second evaluation committee meeting: 4 June 2025
- Details of membership of the evaluation committee are given in section 4

1 Recommendations

1.1 Natalizumab (originator and biosimilar) should not be used to treat relapsing–remitting multiple sclerosis (MS) that is highly active despite a full and adequate course of at least 1 disease-modifying therapy in adults.

1.2 This recommendation is not intended to affect treatment with natalizumab (originator or biosimilar) that was started in the NHS before this guidance was published. People having treatment outside this recommendation 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 relapsing–remitting MS in NICE's technology appraisal guidance on natalizumab for the treatment of adults with highly active relapsing–remitting MS.

What this means in practice

Natalizumab is not required to be funded in the NHS in England to treat highly active relapsing–remitting MS after at least 1 disease-modifying therapy in adults. It should not be used routinely in the NHS in England.

This is because the available evidence does not suggest that natalizumab is value for money.

Why the committee made these recommendations

Usual treatment for highly active relapsing–remitting MS 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 be highly similar and clinically equivalent to natalizumab originator.

Natalizumab (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 have a similar efficacy to these treatments.

There are uncertainties in the economic model, including:

- the source of the data informing progression of MS and risk of death
- how often people have natalizumab.

Because of the uncertainties in the economic model, it is not possible to determine the most likely cost-effectiveness estimates for natalizumab. So, natalizumab should not be used.

2 Information about natalizumab

Marketing authorisation indication

2.1 Natalizumab originator (Tysabri, Biogen) and natalizumab biosimilar (Tyruko, Sandoz) are indicated 'as 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 is available in the summary of product characteristics for natalizumab originator.

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

Price

2.4 The list price for natalizumab originator is:

- £1,130 per 300 mg/15 ml concentrate for solution for intravenous infusion vials (excluding VAT; BNF online, accessed February 2025).
- £1,130 per 2 x 150 mg syringe for subcutaneous injection (company submission).

2.5 The list price for 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 natalizumab originator and natalizumab biosimilar have commercial arrangements. This makes natalizumab available to the NHS with a discount and it would have also applied to this indication if natalizumab had been recommended. The size of each discount is commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence from a number of sources. 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 appraisal, 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 relapsing–remitting multiple sclerosis 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 considered that this was an appropriate definition of highly active disease for the purpose of this appraisal. 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 when pregnant or planning a pregnancy. The patient expert highlighted that people with MS found it empowering to have multiple treatment options that controlled relapses, while still allowing them to do normal daily activities and plan a pregnancy. The committee also noted that natalizumab originator was available in an intravenous and subcutaneous form. This could be beneficial for some people, particularly those with poor venous access. The committee concluded that natalizumab would be a welcome additional treatment option for people with highly active RRMS.

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 originator and biosimilar natalizumab 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 but some people may have cladribine. So, the committee concluded that ocrelizumab, ofatumumab and cladribine are relevant comparators.

- The companies noted that alemtuzumab was 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 is not a relevant comparator.
- Glatiramer acetate and interferon beta 1a and 1b were 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 are not relevant comparators.
- The company that makes natalizumab originator said that AHSCT was 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 is 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 are 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 is a relevant comparator.

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 with over 2 years.
- Saida 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. The TOP study, 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 the TOP study. 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 concluded that people should understand

the risk of developing PML before starting natalizumab and should have regular anti-JCV antibody level tests before and during treatment.

Overview of the network meta-analysis

3.6 The EAG did a systematic review to identify clinical evidence for natalizumab originator and biosimilar and their 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 difference in outcomes for originator and biosimilar natalizumab.

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, 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 considered 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 appraisal. It acknowledged that including all teriflunomide trials would better connect the network, but explained that it had explored this in a scenario with 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. suggested comparable efficacy for ARR and CDP6 for natalizumab, ocrelizumab and ofatumumab (see section 3.6). So, it considered it appropriate to assume equivalent efficacy between these treatments and appraise natalizumab (originator and biosimilar) through a cost-comparison approach. The clinical experts noted that natalizumab has a more rapid onset of action compared with ocrelizumab and ofatumumab. They considered that natalizumab may have slightly improved efficacy outcomes compared with ocrelizumab and ofatumumab, but they considered that this is very uncertain. The committee acknowledged that the NMAs by Samjoo et al. and by the EAG suggested that efficacy outcomes for natalizumab, ocrelizumab and

ofatumumab were similar. It considered that a cost comparison with natalizumab, ocrelizumab and ofatumumab could be an informative scenario and should be provided at consultation. But, overall, it considered that there was not sufficient evidence to confirm that there was no difference in efficacy for natalizumab, ocrelizumab and ofatumumab. It noted that cladribine and ublituximab were also relevant comparators. So, the committee preferred to use the EAG's NMA to inform the efficacy estimates for natalizumab and comparators, rather than using a cost-comparison approach assuming equal efficacy.

Economic model

EAG's modelling approach

3.8 The EAG developed the economic model for this appraisal. 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:

- Expanded Disability Status Scale (EDSS) score increase and decrease
- 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 was challenging within the constraints of a Markov model (see section 3.14). The committee acknowledged that a DES model addressed some of the limitations of a Markov model in reflecting the natural history of MS. It concluded that the EAG's DES model was appropriate for decision making.

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 (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 considered 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 RRMS appraisals 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 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 considered 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 is because in previous RRMS appraisals that used these databases, people with MS experienced faster disease progression, and 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 experience 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 was 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. The committee acknowledged there may be some issues with missing data and the generalisability of the MS Register data to NHS clinical practice, but agreed that these issues would likely also apply to the Canadian databases. NICE's real-world evidence framework provides guidance on assessing data quality. The committee noted that it had not been presented with scenarios that used the MSBase, BCMS or London Ontario MS databases for natural history data. It agreed that it would be helpful to see a completed Data Suitability Assessment Tool (DataSAT) for the MS Register to allow it to assess its suitability to model disease natural history in this appraisal. It also agreed that a DataSAT should be completed for the BCMS and London Ontario MS databases. But it noted that, based on the currently available evidence, the MS Register was the most recent and relevant data source for natural history data and captured the gradual progression of highly active RRMS with high-efficacy disease-modifying therapies.

Progression to secondary-progressive MS

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, 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 overestimate time to secondary-progressive MS compared with the UK population. This was because the MS Register overrepresented older people with MS, who

were more likely to have progressed to secondary-progressive MS. So, the committee agreed that it would be useful to see the predicted proportion with secondary-progressive MS at 5, 10 and 15 years after entering the model to validate the clinical plausibility of the model outcomes. It also noted that the progression to secondary-progressive MS was not assumed to be treatment specific in the EAG's model. The EAG highlighted that this approach aligned with clinical expert advice it had received and other technology appraisals in RRMS. The clinical experts highlighted at the committee meeting that there was no evidence on the time to secondary-progressive MS progression after having specific treatments from clinical trials. They explained that this is because it takes 25 to 30 years for people with RRMS to develop secondary-progressive MS. But, in their experience, treatment choice may impact time to progression to secondary-progressive MS. So, the committee considered that the transition to secondary-progressive MS was likely to be treatment specific, especially given the varying efficacy of available disease-modifying therapies. It acknowledged the challenges in collecting this data, but agreed that this was an area of uncertainty. It agreed that further data on the predicted proportion with secondary-progressive MS at 5, 10 and 15 years in the EAG's model should be provided at consultation.

Efficacy assumptions for intravenous natalizumab originator and biosimilar

3.12 The EAG included intravenous natalizumab originator and biosimilar separately in the NMA (see section 3.6). It then modelled intravenous natalizumab 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, because clinical trials in biosimilars are small and focused on meeting regulatory requirements, the biosimilar is at a disadvantage if considered as a separate product. So, the company

considered that intravenous natalizumab originator and biosimilar should be modelled as equally effective and should differ only in costs. The clinical experts explained that biosimilars were considered clinically equivalent and interchangeable with the originator in clinical practice. The committee noted that the EAG had provided a scenario in which natalizumab originator and biosimilar were considered to have equal efficacy and to differ only in costs. The committee concluded that it was appropriate to assume clinical equivalence between natalizumab originator and biosimilar.

Treatment waning

3.13 The EAG's model used stopping treatment because of adverse events as a proxy for treatment waning. The stopping rates 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 RRMS appraisals. 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 considered 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. The committee thought that the rate of treatment waning was uncertain and may not be represented by stopping treatment because of adverse events. Also, because natalizumab originator and biosimilar should be

considered equally effective, it agreed that the same source for treatment waning should apply to each. The committee concluded that the modelling of treatment waning should be informed by evidence and that the companies and EAG should explore alternative approaches at consultation.

Subsequent treatments in the model

3.14 The EAG's model included subsequent treatments for people who stopped natalizumab or comparators. 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 there was an equal likelihood of having any available subsequent treatment. This was because it was unable to find evidence on treatment sequencing from the literature or the MS Register. 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 noted that ofatumumab had not been included as a subsequent treatment for people with RRMS in the EAG's base case, despite being listed in NHS England's treatment algorithm for MS disease-modifying therapies. 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. Previous 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 considered that the ability of the EAG's model to include subsequent treatments was a considerable improvement on previous RRMS models. But it noted that the EAG's

model assumed that there was an equal likelihood of having any available subsequent treatment in the model, which was not aligned with clinical expert opinion at the committee meeting. So, the committee concluded that it would be helpful to have further data, for example, from real-world evidence sources or clinician surveys, with more information about subsequent treatments in NHS clinical practice.

Stopping treatment at high EDSS scores

3.15 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, which recommend that treatment in RRMS is stopped once people are unable to walk. The EAG updated its model after consultation to apply a stopping rule at EDSS score 7. The committee agreed this was appropriate.

Mortality

3.16 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 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, using 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 1.6 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. (2018) 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 considered 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 a large effect on the overall mortality rate. The clinical experts highlighted a more recent Icelandic study by Eliasdottir et al. (2023) that reported mortality data for people with RRMS. They noted that this data was more aligned with the SMRs in Sadovnick et al. than in Harding et al. But the committee was concerned that the data in Sadovnick et al. was old and collected before disease-modifying therapies were licensed in Canada. So, these people were likely to have higher mortality than expected with current high-efficacy disease-modifying therapies. It noted that this also applied to a proportion of people in Harding et al., which started data collection in 1985. It acknowledged that Harding et al. may have overestimated mortality rates compared with the current population with RRMS in the NHS. But it noted that Harding et al. presented the SMR based on people's EDSS score at death instead of at baseline, as reported in Eliasdottir et al. It considered that people who die of MS-related causes are likely to be those who progress rapidly through EDSS scores, so considering the EDSS score at death was likely more appropriate. The committee agreed that the exact excess mortality for RRMS was uncertain. The committee said that the EAG should provide additional analyses at consultation to verify the plausibility of the proposed

mortality sources. It said that these analyses should include but not be limited to:

- Validating the current estimates with data from the MS Register, which reported a small number of carer-reported deaths. Although not robust enough to inform the model, the committee agreed that the data on EDSS score for people who died in the MS Register could be compared to the SMRs reported in Sadovnick et al. and Harding et al. to determine the plausibility of each source.
- Using the SMRs from Harding et al. as an indication of the relative difference between the EDSS scores but calibrating to a more plausible overall SMR estimate (for example, Jick et al.).

It also agreed that the survival curves from the model should be presented after consultation. The committee concluded that the excess mortality for RRMS was uncertain but that mortality did increase for people with more severe disease. Given the options presented to it, it preferred to use Harding et al. to inform decision making because it was recent UK-specific data with more granular classifications for EDSS scores. But it agreed that further approaches to modelling mortality should be explored at consultation.

Utility values

Source of utility values

3.17 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 NICE's technology appraisal guidance on ponesimod for treating relapsing–

remitting MS. 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

3.18 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 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, particularly in women, trans men and non-binary people who are pregnant. 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 have natalizumab every 6 weeks, and some people who do not have anti-JCV antibodies also 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 those with a high body weight. The committee noted that the risk of developing PML is significantly reduced with 6-weekly dosing. The EAG provided an extreme scenario in which 6-

weekly dosing was used for everyone having natalizumab originator and biosimilar, regardless of the administration route. The committee concluded that a proportion of people having natalizumab in the model should have extended interval dosing. It thought that a scenario in which 60% of people having natalizumab had 6-weekly dosing in the model would be useful. But it agreed that further evidence should be provided on the exact proportion having extended interval dosing with natalizumab in the NHS for rapidly evolving severe RRMS.

Costs for anti-JCV antibody testing

3.19 The committee recalled that anti-JCV antibody tests are needed before starting natalizumab and every 6 months after 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 free anti-JCV tests 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 this was inappropriate, highlighting that there were no known issues in accessing the relevant tests. The clinical experts at the committee meeting confirmed that there is no NHS-funded anti-JCV antibody test available, so the companies' tests are always used in clinical practice. The committee agreed that the costs of anti-JCV antibody testing should be excluded from the model for both natalizumab originator and biosimilar.

Resource use

Natalizumab administration routes

3.20 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. 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 committee meeting noted that in secondary care it is more efficient to administer subcutaneous natalizumab than intravenous natalizumab. But they considered that the overall time saving with subcutaneous natalizumab was minimal. The company that makes natalizumab originator highlighted that it funds a home administration service by a nurse for subcutaneous natalizumab originator. 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. The committee agreed that the company that makes natalizumab originator should submit evidence at consultation to support the use of home administration in the NHS. It advised that it would be helpful to have further information quantifying the difference in resource requirements between subcutaneous and intravenous administration. The committee noted that subcutaneous administration of natalizumab was declining and clinical expert opinion is that home administration is rarely used in the NHS. Based on the available information and clinical expert opinion, the committee concluded that it was appropriate to model equivalent resource use for subcutaneous and intravenous administration.

Cost-effectiveness estimates

Net monetary benefit

3.21 Cost effectiveness was assessed by calculating incremental net monetary benefit (NMB) instead of the incremental cost-effectiveness ratio (ICER). This is 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 originator and intravenous biosimilar natalizumab using its preferred assumptions, with other MS treatments, at threshold values of £20,000 and £30,000 per quality-adjusted life year (QALY) gained. This resulted in a negative incremental NMB. This means that natalizumab is not cost effective in any form compared with the EAG's preferred comparators at £30,000 per QALY gained.

Committee preferred assumptions and analyses

3.22 There were a number of inputs where further data and analyses would help inform the committee's preferred assumptions (see section 3.23). But based on the available evidence, its 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)
- assuming equal clinical effectiveness for natalizumab originator and biosimilar (see section 3.12)
- using the EAG's base-case assumption for treatment waning but exploring further ways to model treatment-effect waning (see section 3.13)
- including ofatumumab, ocrelizumab and ublituximab as subsequent treatment options, ideally with some evidence-based estimate for apportioning the percentage of people having each (see section 3.14)
- using mortality data from Harding et al., while noting the uncertainty in this estimate (see section 3.16)

- including 6-weekly dosing for 60% of people having natalizumab (see section 3.18)
- excluding the costs of anti-JCV antibody testing for both natalizumab originator and biosimilar (see section 3.19)
- assuming equal costs and resource use for subcutaneous and intravenous natalizumab (see section 3.20).

The committee was not presented with analyses that included all of its preferred assumptions. The committee decided that there was considerable uncertainty around several of its preferred assumptions, including the most appropriate way to model mortality, treatment waning and the dosing regimen for natalizumab used in the NHS. Because of this, it could not determine a threshold for cost effectiveness.

Uncertainties to explore further in the modelling

3.23 There was a high level of uncertainty surrounding some of the assumptions in the model. The committee noted concerns from the company that makes natalizumab originator that the information provided by the EAG on model inputs, outputs and assumptions was insufficient for full external model validation. The committee acknowledged that this could further increase the uncertainty around the cost-effectiveness results. It agreed that further information should be provided at consultation on the following:

- any relevant information regarding the clinical equivalence of natalizumab originator and biosimilar
- a scenario assuming equal clinical effectiveness for natalizumab, ocrelizumab and ofatumumab (see section 3.7)
- additional information on the quality and relevance of the data from the MS Register, including completion of the DataSAT tool in NICE's real-world evidence framework for all potential data sources (see section 3.10)

- the proportion of people with secondary-progressive MS in the model at 5, 10 and 15 years (see section 3.11)
- exploring alternative ways to model treatment waning (see section 3.13)
- data on subsequent treatments had in NHS clinical practice (see section 3.14)
- exploring alternative ways to model mortality, including but not limited to:
  - using data from the MS Register to verify the plausibility of the data by Sadovnick et al. and Pokorski et al.
  - using the SMRs from Harding et al. as an indication of the relative difference between the EDSS scores but calibrating to a more plausible overall SMR estimate MS (see section 3.16)
- survival curves showing predicted survival in the model (see section 3.16)
- data on the proportion of people having 6-weekly dosing with natalizumab for each formulation in NHS clinical practice (see section 3.18)

Managed access

Recommendation with managed access

3.24 Having concluded that natalizumab originator and biosimilar could not be recommended for routine use, the committee considered whether they could be recommended with managed access for treating highly active RRMS. It noted that the neither company had submitted a managed access proposal, so it could not make a recommendation for managed access at this stage.

Other factors

Equality

3.25 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 women than men. The committee noted that the issue of sex-related disease prevalence could not be addressed in a technology appraisal.
- The committee noted that the onset of MS may coincide with family planning and that most high-efficacy disease-modifying therapies cannot be used when pregnant or planning a pregnancy. 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 considered this in its decision making.
- 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 is 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 those for whom travelling is difficult, or who have more limited access to transport. The committee recalled that subcutaneous natalizumab is normally administered in secondary care (see section 3.20). So it considered that this is not an equality issue for the is appraisal.

Conclusion

Recommendation

3.26 The committee concluded that there were uncertainties in the cost-effectiveness evidence. This meant that it was not possible to determine

the most likely cost-effectiveness estimates for natalizumab originator and biosimilar. So, they should not be used.

4 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.

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