NICE National Institute for Health and Care Excellence

NICE guidance

Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis

Technology appraisal guidance
Published: 22 August 2007
Last updated: 21 May 2024

www.nice.org.uk/guidance/ta127

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

1.1 Natalizumab (branded or biosimilar) is recommended as an option for the treatment only of rapidly evolving severe relapsing–remitting multiple sclerosis (RES-RRMS) in adults. RES-RRMS is defined by 2 or more relapses in the previous year, and baseline MRI evidence of disease activity.

1.2 This recommendation is not intended to affect treatment with natalizumab 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.

2 The technology

2.1 Natalizumab (branded and biosimilar) has a marketing authorisation as a single disease-modifying therapy in highly active relapsing–remitting multiple sclerosis for the following groups.

- Patients with rapidly evolving severe relapsing–remitting multiple sclerosis defined by 2 or more disabling relapses in 1 year, and 1 or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI. This patient group is referred to as the 'RES group'.
- Patients with high disease activity despite treatment with beta interferon. This group is defined as patients who have failed to respond to a full and adequate course of a beta interferon. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintensive lesions in cranial MRI or at least 1 gadolinium-enhancing lesion. This patient group is referred to as the 'suboptimal therapy group'.

2.2 All antilymphocyte monoclonal antibodies should be given under the supervision of an experienced specialist, in an environment where full resuscitation facilities are immediately available. The use of natalizumab may be associated with infections, urticaria, headache, dizziness, vomiting, nausea, arthralgia, infusion reactions and hypersensitivity reactions. Natalizumab has also been associated with an increased risk of progressive multifocal leukoencephalopathy (PML). For full details of side effects and contraindications, see the summary of product characteristics.

2.3 Natalizumab is administered by intravenous infusion; the recommended dose is 300 mg every 28 days. The list price of branded natalizumab (Tysabri, Biogen Idec and Elan Pharma International Ltd) is £1,130 per 300 mg vial (excluding VAT; BNF edition 86). Costs may vary in different settings because of negotiated procurement discounts. Prices paid for branded or biosimilar natalizumab should be no higher than that provided through the branded list price, and should be in line with any future national procurement outcome.

3 The manufacturer's submission

The appraisal committee considered evidence submitted by the manufacturer of natalizumab and a review of this submission by the evidence review group (ERG).

3.1 In its submission, the manufacturer compared natalizumab with beta interferon, glatiramer acetate and best supportive care (that is, no active treatment) for both the RES and the suboptimal therapy groups. The 2 major clinical outcomes examined were disability progression, defined as an increase in the expanded disability status scale (EDSS) score sustained for 12 or 24 weeks at 2 years, and annualised relapse rate.

3.2 The manufacturer presented data from the multinational, double-blind, randomised AFFIRM study (n=942), which compared natalizumab with placebo. The study comprised people with relapsing–remitting multiple sclerosis, of which a subgroup had highly active relapsing–remitting multiple sclerosis. A post-hoc subgroup analysis of AFFIRM (n=209) provided clinical data for the RES group. The marketing authorisation for the suboptimal therapy group was based on data from the SENTINEL study (n=1,171), which compared natalizumab and beta interferon with beta interferon alone. However, the combination of natalizumab with beta interferon is not included in the marketing authorisation for natalizumab because of concerns over the risk of PML, and data from the SENTINEL study were not presented by the manufacturer. Instead, the manufacturer assumed that the intention-to-treat (ITT) population from AFFIRM is a suitable proxy for the suboptimal therapy group. The manufacturer provided additional data from 2 phase 2 studies. The manufacturer did not identify any studies that compared natalizumab with beta interferon or glatiramer acetate.

3.3 The AFFIRM study demonstrated that natalizumab statistically significantly reduces the probability of sustained disability progression compared with placebo in both the ITT and RES populations. The hazard ratios (HRs) varied between 0.46 and 0.58 in the ITT population, depending on the measure of disability progression (increase in EDSS sustained for 24 and 12 weeks respectively), and between 0.36 and 0.47 in the RES group. In addition, natalizumab led to a reduction in relapse rate, with a relative risk reduction of 0.68 in the ITT population and 0.81 in the RES group. The manufacturer presented

evidence that showed that, compared with placebo, natalizumab significantly improved health-related quality of life when measured with the SF-36 instrument, although not when the MSQLI instrument was used.

3.4 Given the absence of study data comparing natalizumab directly with beta interferon and glatiramer acetate, the manufacturer carried out an indirect comparison. This adopted an existing method to compare the results of AFFIRM with systematic reviews of beta interferon and glatiramer acetate. The systematic reviews included people with relapsing–remitting multiple sclerosis rather than highly active relapsing–remitting multiple sclerosis and did not specifically examine the clinical effectiveness of the drugs in the RES or suboptimal therapy groups. Therefore, the manufacturer assumed that the treatment effect of beta interferon and glatiramer acetate in relapsing–remitting multiple sclerosis was equivalent to that in the RES and suboptimal therapy groups. The results of the indirect analysis showed that natalizumab was associated with a statistically significant reduction in relapse rates compared with beta interferon and glatiramer acetate, with relative risks of 0.63 and 0.57 respectively for the ITT population and 0.49 and 0.43 respectively for the RES group. The results of the indirect analysis for disability progression were submitted to NICE in confidence.

3.5 The AFFIRM study showed that natalizumab is not associated with a higher incidence of adverse events than placebo. The indirect comparison performed by the manufacturer found no statistically significant differences in adverse events between natalizumab and glatiramer acetate. However, compared with beta interferon, natalizumab was found to be associated with a statistically significant reduction in the incidence of influenza-like symptoms and myalgia or arthralgia, with relative risks of 0.47 and 0.68 respectively.

3.6 The manufacturer presented a multistate Markov model based on the economic model developed by the School of Health and Related Research (ScHARR) at Sheffield University that was used in NICE's previous technology appraisal guidance on beta interferon and glatiramer acetate for the treatment of multiple sclerosis (now replaced by NICE's technology appraisal guidance on beta interferons and glatiramer acetate). The manufacturer's model predicts disability progression and disease activity over a time horizon of 20 years using a series of 1-year cycles. The model took an NHS perspective for the majority of costs, but

included carers' disutility in the base case.

3.7 The clinical data that populate the manufacturer's model come from the AFFIRM study and the systematic reviews of beta interferon and glatiramer acetate. Additional data on disability progression were derived from the London Ontario data set (a longitudinal study of more than 1,000 people with relapsing–remitting multiple sclerosis followed for a mean of 25 years). Data on costs and utilities (based on EQ-5D scores) associated with EDSS states were derived from a cross-sectional study (the UK MS survey) commissioned by the manufacturer. This survey included people with relapsing–remitting, secondary progressive and primary progressive multiple sclerosis, and the results were based on 2,048 responses (a 15.8% response rate).

3.8 The results of the manufacturer's analysis showed that the incremental cost-effectiveness ratios (ICERs) for the RES group compared with best supportive care, beta interferon and glatiramer acetate were £44,600, £32,000 and £34,600 per quality-adjusted life year (QALY) gained respectively. For the suboptimal therapy group the ICERs were £56,100, £43,400 and £44,300 per QALY gained respectively.

3.9 Sensitivity analysis demonstrated that the variables that had the greatest effect on the ICERs were the time horizon over which costs and outcomes are evaluated and changing the source of the disability progression data from AFFIRM to the London Ontario dataset. Extending the time horizon to 30 years, for example, reduced the ICERs for natalizumab versus beta interferon to £24,600 and £34,200 per QALY gained in the RES and suboptimal therapy groups respectively. In contrast, changing the source of the disability progression data from AFFIRM to the London Ontario dataset increased the ICERs to £42,300 and £55,300 per QALY gained for natalizumab versus beta interferon in the RES and suboptimal therapy groups respectively.

3.10 The ERG expressed a number of concerns about the manufacturer's submission. The ERG recognised the general uncertainty associated with indirect analyses and that the data for the comparators was derived from people with relapsing–remitting multiple sclerosis rather than highly active relapsing–remitting multiple sclerosis. The ERG stated that this might alter the conclusions of the analysis, although the magnitude and direction of any such effect was unknown.

3.11 The ERG recognised that the approach adopted by the manufacturer in its economic modelling was pragmatic given the absence of better quality data. However, it expressed concern about the extrapolation of 2-year data from the AFFIRM study to a 20-year time horizon. The ERG also expressed concern that the utility and cost data, which were based on the UK MS survey, were not exclusively derived from people with highly active relapsing–remitting multiple sclerosis; in addition, the survey may not have been representative because of the low response rate.

3.12 The ERG commented on the limitations of the EDSS instrument, which suffers from limited responsiveness and inter- and intra-rater variability. In addition, the ERG expressed concern that, although the transition probabilities in the manufacturer's model were based on data from AFFIRM, the model appeared to predict a higher rate of sustained disability progression at 2 years than reported in AFFIRM. The ERG stated that this might overestimate the effectiveness of natalizumab, and might therefore lead to more favourable ICERs in the model. The ERG also highlighted the limited evidence for the assumption in the manufacturer's model that natalizumab reduces progression from relapsing–remitting multiple sclerosis to secondary progressive multiple sclerosis.

3.13 Full details of all the evidence are in the manufacturer's submission and the ERG report.

4 Consideration of the evidence

4.1 The appraisal committee reviewed the data available on the clinical and cost effectiveness of natalizumab for highly active relapsing–remitting multiple sclerosis, having considered evidence on the nature of the condition and the value placed on the benefits of natalizumab by people with multiple sclerosis, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.

Clinical effectiveness

4.2 The committee considered the data on the clinical effectiveness of natalizumab in the subgroup of people whose multiple sclerosis has failed to respond to treatment with beta interferon, that is, the suboptimal therapy group. It noted that the ITT population from the AFFIRM study, which showed that natalizumab significantly reduces relapse rate and delays disability progression compared with placebo, was used in the manufacturer's submission as a proxy for this group. The committee was aware that the SENTINEL study was used to inform the licence for the suboptimal therapy group but that the study considered the use of natalizumab in combination with beta interferon; this combination is not licensed because of safety concerns. The committee noted that there is no direct evidence about the clinical effectiveness of natalizumab monotherapy in the suboptimal therapy group. In addition, the clinical experts confirmed that, although natalizumab may be used in this situation, there are no clinical study data to indicate how clinically effective it is in this group. The committee therefore concluded that the clinical effectiveness of natalizumab in the suboptimal therapy group has not been fully established.

4.3 The committee considered the data on the clinical effectiveness of natalizumab in the RES group. The committee was aware that a post hoc analysis of the AFFIRM study population indicated that natalizumab significantly reduces relapse rate and delays disability progression compared with placebo in the RES group. It noted the results of an indirect analysis performed by the manufacturer showing that natalizumab reduces relapse rate more effectively than beta interferon or

glatiramer acetate. The committee also heard the views of the clinical and patient experts that natalizumab has a clinically important effect on disability progression in people with highly active forms of multiple sclerosis that has not been seen with other disease-modifying therapies. The committee agreed that natalizumab is clinically effective in the RES group compared with placebo, beta interferon and glatiramer acetate.

Cost effectiveness

4.4 Although the committee had reservations about the data on the clinical effectiveness of natalizumab in the suboptimal therapy group (as indicated in section 4.2), it reviewed the manufacturer's cost-effectiveness analysis for this group and the ERG's comments. The committee noted that the base case ICERs estimated by the manufacturer for the suboptimal therapy group were £43,400 per QALY gained or higher. It therefore concluded that natalizumab would not be a cost-effective use of NHS resources in this group of people.

4.5 The committee noted that the base case ICERs estimated for the RES group by the manufacturer ranged from £32,000 per QALY gained (natalizumab compared with beta interferon) to £44,600 per QALY gained (natalizumab compared with best supportive care).

4.6 The committee considered which of the comparators used in the manufacturer's cost-effectiveness analysis for the RES group best reflected current clinical practice. The committee noted that, as described in NICE's technology appraisal guidance 32, beta interferon and glatiramer acetate were not recommended by NICE for the treatment of multiple sclerosis on the basis of their cost effectiveness. However, it was aware that, following NICE's assessment of beta interferon and glatiramer acetate, a risk-sharing scheme had been set up by the Department of Health. This allowed the continued use of these technologies with the financial risk being shared between the NHS and the participating pharmaceutical companies. The committee also noted the information from consultees that treatment with beta interferon is the current standard of practice in the RES group. It was persuaded, therefore, that the most appropriate comparator for determining cost effectiveness in the RES group is beta interferon.

4.7 The committee noted the views of the ERG that the results of the manufacturer's economic model were associated with considerable uncertainty and that alternative assumptions would substantially increase or decrease the ICERs (see sections 3.9 and 3.12). However, the committee concluded that the ICER of £32,000 per QALY for natalizumab compared with beta interferon presented by the manufacturer was more likely to be an overestimate. The committee considered that, for a disease which presents in early life and has limited effect on life expectancy, a time horizon longer than 20 years would be appropriate, which would lower the ICER. In addition, it was persuaded that the disutility of relapses may have been underestimated in the model. In addition, the committee took into account the high degree of clinical need among people in the RES group and the innovative nature of the technology. The committee therefore concluded that the use of natalizumab for people with RES would be a cost-effective use of NHS resources and that it should be recommended for use within the NHS for the treatment of people with RES.

5 Implementation

5.1 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 3 months of its date of publication.

5.2 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 2 months of the first publication of the final draft guidance.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has highly active relapsing–remitting multiple sclerosis and the healthcare professional responsible for their care thinks that natalizumab is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Recommendations for further research

6.1 The committee considered that further research into the clinical effectiveness of natalizumab for the treatment of highly active relapsing–remitting multiple sclerosis in the suboptimal therapy group is needed.

7 Appraisal committee members and NICE project team

Appraisal committee members

The Appraisal committee is a standing advisory committee of NICE. Its members are appointed for a 3-year term. The appraisal committee meets twice a month except in December, when there are no meetings. The committee membership is split into 3 branches, with the chair, vice chair and a number of other members attending meetings of both branches. Each branch considers its own list of technologies, and ongoing topics are not moved between the branches.

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

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

The following is a list of the committee members who took part in the discussions for this appraisal.

Professor Keith Abrams
Professor of Medical Statistics, University of Leicester

Dr Jeff Aronson
Reader in Clinical Pharmacology, Radcliffe Infirmary

Dr Darren Ashcroft
Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Professor David Barnett (Chair)
Professor of Clinical Pharmacology, University of Leicester

Dr Peter Barry
Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Professor Stirling Bryan
Director of the Health Economics Facility, University of Birmingham

Professor John Cairns
Public Health and Policy,London School of Hygiene and Tropical Medicine

Dr Mark Charkravarty
Head of Government Affairs and NHS Policy, Procter and Gamble Pharmaceuticals (UK)

Professor Jack Dowie
Health Economist, London School of Hygiene and Tropical Medicine

Lynn Field
Nurse Director, Pan Birmingham Cancer Network

Professor Christopher Fowler
Professor of Surgical Education, University of London

Dr Fergus Gleeson
Consultant Radiologist, Churchill Hospital, Oxford

Ms Sally Gooch
Former Director of Nursing and Workforce Development, Mid Essex Hospitals Services NHS Trust

Mrs Barbara Greggains
Lay member

Mr Sanjay Gupta
FormerStroke Services Manager, Basildon and Thurrock Universities Hospitals NHS Trust

Dr Mike Laker
Medical Director, Newcastle Hospitals NHS Trust

Mr Terence Lewis

Mental Health Consultant, National Institute for Mental Health in England

Professor Gary McVeigh
Professor of Cardiovascular Medicine, Queens University, Belfast

Dr Ruairidh Milne
Senior Lecturer in Health Technology Assessment, National Coordinating Centre for Health Technology

Dr Neil Milner
General Medical Practitioner, Sheffield

Dr Rubin Minhas
General Practitioner, CHD Clinical Lead, Medway PCT

Dr John Pounsford
Consultant Physician, North Bristol NHS Trust

Dr Rosalind Ramsay
Consultant Psychiatrist, Adult Mental Health Services, Maudsley Hospital, London

Dr Stephen Saltissi
Consultant Cardiologist, Royal Liverpool University Hospital

Dr Lindsay Smith
General Practitioner, East Somerset Research Consortium

Mr Cliff Snelling
Lay member

Dr Ken Stein
Senior Lecturer, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Professor Andrew Stevens
Professor of Public Health, University of Birmingham

NICE project team

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

Zoe Charles and Prashanth Kandaswamy
Technical Leads

Dr Elisabeth George
Technical Adviser

Reetan Patel
Project Manager

8 Sources of evidence considered by the committee

The evidence review group (ERG) report for this appraisal was prepared by Peninsula Technology Assessment Group, University of Exeter:

- Ruth Garside, Colin Green, Martin Hoyle, et al. (2007) The effectiveness and cost effectiveness of natalizumab for multiple sclerosis: an evidence review of the submission from Biogen.

The following company or sponsor provided a submission for this appraisal:

- Biogen Idec UK and Elan Pharma International

The following organisations accepted the invitation to participate in this appraisal. They are also invited to comment on the appraisal consultation document and supporting evidence. Consultee organisations have the opportunity to appeal against the final appraisal determination.

Professional or specialist, patient or carer groups, and other organisations:

- Association of British Neurologists
- Multiple Sclerosis Society
- Multiple Sclerosis Trust
- Primary Care Neurology Society
- Royal College of Nursing
- Royal College of Physicians
- UK Multiple Sclerosis Specialist Nurse Association
- Department of Health
- Oldham PCT
- Welsh Assembly Government

Commentator organisations (without the right of appeal):

- Amgen (mitoxantrone)
- Biogen Idec UK (interferon beta-1a)
- British National Formulary
- Department of Health, Social Services and Public Safety for Northern Ireland
- Medicines and Healthcare products Regulatory Agency (MHRA)
- Multiple Sclerosis Group, University of Bristol
- National Coordinating Centre for Health Technology Assessment
- National Collaborating Centre for Chronic Conditions
- NHS Quality Improvement Scotland
- Peninsula Technology Assessment Group, University of Exeter
- Schering Health Care (interferon beta-1b)
- Serono (interferon beta-1a)
- Teva Pharmaceuticals (glatiramer acetate).

The following individuals were selected from clinical specialist and patient advocate nominations from the professional or specialist, and patient or carer groups. They gave their expert personal view on natalizumab for the treatment of multiple sclerosis by providing written evidence to the committee. They are invited to comment on the appraisal consultation document:

- Professor David Miller, nominated as a clinical expert by the Association of British Neurologists.
- Professor Alan Thompson, nominated as a clinical expert by the Multiple Sclerosis Society.
- Megan Burgess, nominated as a clinical expert by the Royal College of Nursing.
- Mrs Caroline Haynes, nominated as a patient expert by the MS Trust.

- Mr Mark Priest, nominated as a patient expert by the MS Trust.

Update information

May 2024: The wording in recommendation 1.1 has been updated to address concerns raised by the clinical community and company that the previously used definition of rapidly evolving severe multiple sclerosis (RES) was overly restrictive. This is because the requirement for 2 MRI scans places significant burden on a limited diagnostic and monitoring resource. The wording has now been changed to better reflect clinical practice.

November 2023: The wording in recommendation 1.1 and section 2 has been updated to include procurement information about natalizumab biosimilars.

March 2014: Implementation section was updated to clarify that natalizumab is recommended as an option for treating highly active relapsing–remitting multiple sclerosis.

ISBN: 978-1-4731-6144-3