

**Clinical Commissioning Policy:
Disease Modifying Therapies for
Patients with Multiple Sclerosis (MS)**

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Clinical Commissioning Policy: Disease Modifying Therapies for Patients with Multiple Sclerosis (MS)

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Description	NHS England will commission disease modifying therapies for patients with multiple sclerosis in accordance with the criteria outlined in this document. This policy outlines the arrangements for funding of this treatment for the population in England.
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Document Status

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Policy Statement

NHS England will commission MS treatments in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

Throughout the production of this document, due regard has been given to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited in under the Equality Act 2010) and those who do not share it.

Plain Language Summary

Multiple Sclerosis (MS) is a condition of the central nervous system. In MS the coating around nerve fibres (myelin) is damaged causing a range of symptoms. Approximately 100,000 people in the UK have MS with most people diagnosed between 20-40.

This policy provides guidance on the use of disease modifying therapies for patients with MS. In particular, it identifies starting and stopping criteria for the use of these drugs and clarifies the definitions of the terms used to describe different presentations of MS.

This policy provides definitions to be adopted across England which will allow beta interferon, glatiramer acetate, natalizumab and fingolimod to be commissioned without the need for prior approval.

Information on the outcome of treatments for these patients will be collected and considered when this policy is reviewed.

1. Introduction

Beta-Interferon and Glatiramer Acetate

The National Institute for Health and Clinical Excellence (NICE) produced guidance (NICE Technology Appraisal 32)⁴ for the use of beta interferon and glatiramer acetate which did not recommend them, because although the guidance stated that they work, there remains uncertainty about which patients benefit from these medicines and to what extent. The Department of Health (DH) produced a risk sharing scheme recommending these treatments, and helping ensure that they be made cost effective for the NHS to commission. (DH Health Service Circular HSC 2002/004)². The treatments outlined within this policy for the use of beta interferon and glatiramer acetate follow the recommendations of the HSC (2002/004) circular, which also outlines criteria for the commencement and stopping of disease modifying therapies (beta interferon and glatiramer acetate) for MS.

Natalizumab

Commencement and stopping criteria for natalizumab were added following the publication of NICE Technology Appraisal Guidance 127; Natalizumab for the treatment of adults with highly active relapsing – remitting MS.⁵ This is recommended as a treatment option only for rapidly-evolving severe (RES) relapsing remitting MS.

Fingolimod

"NICE Technology Appraisal 254 was published in April 2012: *Fingolimod for the treatment of highly active relapsing-remitting MS*⁶. Fingolimod is recommended as an option for the treatment of highly active relapsing–remitting MS in adults already receiving beta-interferon. In addition, fingolimod is also recommended for patients who fail glatiramer acetate therapy. Furthermore, fingolimod is also recommended as an alternative to natalizumab for those patients receiving natalizumab who are at high risk of developing progressive multifocal leukoencephalopathy (PML). Data supporting switching to fingolimod from glatiramer acetate and natalizumab was not provided in the manufacturer's submission to NICE, but is based on data that has been acquired subsequent to the NICE approval.

This policy applies to all patients whose responsible commissioner is within the remit of NHS England. Definitions and indications for use of disease modifying drugs in this document are based on the HSC 2002/2004, the Association of British Neurologists (ABN) guidance documents and the Multiple Sclerosis Trust guide 'MS explained'^{1,2,3}.

2. Definitions

Relapse

A relapse is defined as the onset of new symptoms or the worsening of pre-existing

symptoms attributable to demyelinating disease lasting for more than 24 hours and preceded by improving or stable neurological status for at least 30 days from the onset of the previous relapse in the absence of infection, fever or significant metabolic disturbance.¹

Clinically Significant Relapse

All relapses are clinically significant, but in usual practice relapses contributing to the eligibility for Disease Modifying Therapies are:

- Any motor relapse
- Any brainstem relapse
- A sensory relapse if it leads to functional impairment
- Relapse leading to sphincter dysfunction
- Optic neuritis
- Intrusive pain lasting more than 48 hours.

Disabling Relapse

A disabling relapse is defined as any relapse which fulfills one or more of the following criteria:

- Affects the patient's ability to work
- Affects the patient's activities of daily living as assessed by an appropriate method
- Affects motor or sensory function sufficiently to impair the capacity or reserve to care for themselves or others as assessed by an appropriate method
- Needs treatment/hospital admission.¹

Relapsing remitting MS

Patients with a diagnosis of active MS with relapsing onset; active disease is defined by two clinically significant relapses in the previous two years.

Aggressive MS.

Patients with relapsing and remitting MS that is considered to be rapidly evolving and likely to prove severe in due course.¹

Secondary progressive MS.

Following a period of relapsing-remitting MS, the frequency of relapses is decreased and disability increased.³ Disease modifying treatments are only recommended in relapsing secondary progressive MS when relapses are the predominant cause of increasing disability.¹

Primary progressive MS

Disability increases from the outset, usually with the absence of distinct relapses.³
No disease modifying treatment is indicated.¹

Highly active disease

TA254, defines highly active disease as that in patients with an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon.⁶

3. Aim and objectives

This policy aims to:

Provide guidance on the use of disease modifying therapies (beta interferon and glatiramer acetate), fingolimod and natalizumab for patients with MS.

The objectives are:

To identify commencement and stopping criteria for the use of these drugs and to clarify the definitions of the terms used to describe different presentations of MS.

In addition, since NICE issued TA127 (natalizumab) and TA254 (fingolimod) as disease modifying therapies, commencement and stopping criteria for natalizumab and fingolimod in highly active disease have been included in this policy.

4. Epidemiology and needs assessment

See NICE TA32⁴, NICE TA127⁵ and NICE TA254⁶

5. Evidence base

See NICE TA32⁴, NICE TA127⁵ and NICE TA254⁶ for evidence relating to NICE approved indications and use of beta interferon and glatiramer acetate.

Glatiramer acetate to fingolimod switching

In the absence of the head-to-head data between fingolimod and the other treatments, Roskell and colleagues performed a meta-analysis technique using methods to allow an indirect treatment comparisons and found that the relative annualised relapse rate (ARR) glatiramer acetate compared to Fingolimod was 1.43 (95%CI 1.16-1.77)⁸. This finding has recently been replicated using real-world comparative effectiveness study using MSBase⁹ and the FIRST study, which was a fingolimod cardiac safety study¹⁰. In a post-hoc analysis from the pivotal phase 3 FREEDOMS trials it is clear that patients who had received glatiramer acetate prior to initiating fingolimod did as well as subjects who had previously received interferon-beta or were naïve to treatment (data onfile, Novartis)¹¹.

Natalizumab to fingolimod switching

At present there is no head-to-head data between fingolimod and natalizumab¹². Jokubaitis and colleagues, using real-world data in the MSBase register have analysed 89 patients who switched from natalizumab to fingolimod and were followed-up for a median 10 months. There was a small increase in relapse rate on fingolimod (ARR 0.38) relative to natalizumab (ARR 0.26; $p=0.002$)¹². However, there was no evidence of rebound (pre-natalizumab ARR 1.54)¹². In a large fingolimod cardiac safety study 253 patients with MS were switched to fingolimod; 134 had stopped natalizumab more than 6 months before and 119 between 3 and 6 months earlier¹⁰. It is clear that on stopping natalizumab there is rebound disease activity on stopping natalizumab, but these patients respond to treatment with a reduction in the number of relapses over the next 4 months¹⁰.

Internationally, fingolimod has now become the drug of choice for patient MS on natalizumab who are JCV seropositive and are at high-risk of developing PML. There is a risk of carry-over PML when switching from natalizumab to fingolimod therefore neurologists have implemented various protocols with variable washout periods. The assumption is that by allowing CNS immune reconstitution to occur, post-natalizumab, this would limit the risks of PML occurring on fingolimod. It has also become clear that a prolonged natalizumab washout is associated with rebound disease activity^{13,14,15,16}.

6. Rationale behind the policy statement

This policy provides definitions to be adopted across England which will allow beta interferon, glatiramer acetate, natalizumab and fingolimod to be commissioned without the need for prior approval.

7. Criteria for commissioning

The following criteria must be used in conjunction with the definitions in section 2. It is important that the frequency and severity of relapses both in pre and post treatment phases are accurately and consistently recorded so as to ensure meaningful audit. The starting and stopping criteria for the use of beta interferon and glatiramer acetate are based upon the criteria outlined in the Association of British Neurologists (ABN) Guidelines, which can be found in Appendix IV of the DH HSC 2002/04.

A Beta interferon for relapsing remitting disease

A.1 Starting Criteria

All of the following criteria must be met. The patient:

- has had at least 2 clinically significant relapses in previous 2 years*
- is able to walk 10m or more**
- is not pregnant or attempting conception

- is aged over 18 years
- has no contra-indications

* Neurologists may, in certain other circumstances where the evidence for efficacy is less secure, also consider advising treatment after discussion with the patient concerning the risks and benefits. For example;

(i) Patients within 12 months of a clinically significant clinically isolated syndrome when MRI evidence predicts a high likelihood of recurrent episodes (i.e. development of MS).

(ii) patients with only a single major relapse in the preceding two years, but combined with MRI evidence of continuing disease activity (i.e. meet the revised McDonald criteria for MS)

(iii) individuals aged less than 18 with relapsing remitting MS

** For patients who can walk between 10 and 99 m (aided or unaided, EDSS 6.0 to 6.5), treatment with DMTs is permitted but recommended less strongly than for patients able to walk more than 100m unaided (EDSS 5.5 or less).

A.2 Stopping Criteria

Treatment should be stopped if one or more of the following criteria are met:

- No reduction in frequency or severity of relapses compared with pre-treatment phase following a minimum 6 month period of beta interferon treatment, unless the frequency and/or severity of relapses necessitates an earlier change of therapy (e.g. natalizumab)
- Intolerable adverse effects of the drug
- The patient is pregnant, breast feeding or attempting conception
- Development of inability to walk, persistent for more than 6 months, unless unable to walk for reasons other than MS.
- Confirmed secondary progressive disease with an observable increase in disability over a 6 month period (see beta interferon secondary progressive criteria for definitions)
- Stopping criteria should be made known to patients and agreed before treatment is begun.

B Beta interferon for secondary progressive disease

B.1 Starting Criteria

All of the following criteria must be met. The patient:

- has had at least two *disabling relapses* in two years

- is able to walk 10m or more
- has had minimal increase in disability due to gradual progression over the past 2 years
- has had disease progression by less than 2 EDSS point over last year (other than relapse-related), where the data have been recorded
- is not pregnant or attempting conception
- is aged over 18 years
- has no contra-indications

B.2 Stopping Criteria

One or more of the following criteria are met:

- No reduction in frequency or severity of relapses compared with pre-treatment phase following a minimum 6 month period of beta interferon treatment
- Intolerable adverse effects of the drug
- The patient is pregnant, breast feeding or attempting conception
- Development of inability to walk, persistent for more than 6 months, unless unable to walk for reasons other than MS.
- Stopping criteria should be made known to patients and agreed before treatment is begun.

C Glatiramer acetate for relapsing remitting disease

C.1 Starting Criteria

All of the following criteria must be met. The patient:

- has had at least 2 *clinically significant relapses* in previous 2 years
- is able to walk 100m or more without assistance*
- is not pregnant or attempting conception
- is aged over 18 years
- has no contra-indications

*without assistance means that the patient is free standing and does not require walking aids.

C.2 Stopping Criteria

One or more of the following criteria are met:

- No reduction in frequency or severity of relapses compared with pre-treatment phase following a minimum 6 month period of glatiramer acetate
- Intolerable adverse effects of the drug
- The patient is pregnant, breast feeding or attempting conception
- Development of inability to walk, persistent for more than 6 months, unless

unable to walk for reasons other than MS.

- Confirmed secondary progressive disease with an observable increase in disability over a 6 month period

Stopping criteria should be made known to patients and agreed before treatment is begun.

D Glatiramer acetate for secondary progressive disease

Clinical efficacy of Glatiramer Acetate has been limited to reducing relapse rate but not preventing increase in disability. Glatiramer Acetate will not be routinely commissioned for patients with secondary progressive disease.

E Natalizumab for rapidly evolving severe (RES) relapsing-remitting MS

E.1 Starting Criteria

All of the following criteria* must be met. The patient:

- has had two or more disabling relapses in the past year
- has one or more gadolinium-enhancing lesions on MRI or increase in T2 lesion load compared with previous MRI *unless* comparator MRI is unavailable or assessment of gadolinium-enhancement is unreliable as the patient is treated with steroids at around the time of scan.
- has had no previous disease modifying therapy OR is receiving treatment with beta interferon and does not meet the agreed stopping criteria.

*As per NICE Technology Appraisal Guidance 127 patients with high disease activity taking beta interferon or glatiramer acetate but do not fulfil the RES criteria will not be routinely funded for natalizumab.

E.2 Stopping Criteria

One or more of the following criteria are met:

- No reduction in frequency or severity of relapses compared with pre-treatment phase following a minimum 3 month period of natalizumab treatment
- Unacceptable adverse effects of the drug
- The patient is pregnant, breast feeding or attempting conception
- Development of secondary progressive disease causing inability to walk for more than 6 months

Stopping criteria should be made known to patients and agreed before treatment is begun.

F Fingolimod for highly active relapsing – remitting MS

F.1 Starting Criteria

Fingolimod is recommended for the treatment of highly active relapsing–remitting MS in adults, *only* if the following criteria are met:

- Patients have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon* or glatiramer acetate,
- As an alternative to natalizumab for those patients receiving natalizumab who are at high risk of developing progressive multifocal leukoencephalopathy (PML) as defined by the following:
 - JCV exposure indicated by anti-JCV antibody positive status
 - Receiving an immunosuppressant prior to receiving natalizumab
 - Natalizumab treatment duration of >2 years

and

- The manufacturer provides fingolimod with the discount agreed as part of the patient access scheme.

Updated MHRA advice (May 2012)⁷ recommends extended early monitoring of patients before, during and for a minimum 6 hours after the first dose. Specific advice on this extended monitoring is available at:

<http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON152723>

Groups of patients contraindicated to the use of this drug are also identified.

It is recommended that patients who are switched from natalizumab to fingolimod have a wash out period of at least 8 weeks.

*NICE TA254 section 4.6 The Committee ...was unable to make any recommendations for the use of fingolimod in any other populations covered by the marketing authorisation without evidence on the cost effectiveness of fingolimod for these populations from the manufacturer.⁵

F.2 Stopping Criteria (adapted from the stopping criteria for natalizumab)

One or more of the following criteria are met:

- No reduction in frequency or severity of relapses compared with pre-treatment phase following a minimum 3 month period of fingolimod treatment
- Unacceptable adverse effects of the drug
- The patient is pregnant, breast feeding or attempting conception
- Development of secondary progressive disease causing inability to walk for

more than 6 months

Stopping criteria should be made known to patients and agreed before treatment is begun.

8. Patient pathway

Patients must be under the care of a designated MS centre which is registered to take part in the national risk share scheme involving the three beta interferon products and glatiramer.

9. Governance arrangements

See Neuroscience service specification.

10. Mechanism for funding

From April 2013 NHS England is the responsible commissioner for disease modifying therapies in MS. Monitoring of the use of these medicines in accordance with this policy will be expected in the form of audit data.

11. Audit requirements

Providers will be expected to provide information on activity and outcomes on request.

Natalizumab NICE TA127 Audit tool. Available from:

<http://guidance.nice.org.uk/TA127/AuditSupport/doc/English>

Fingolimod NICE TA254 audit tool. Available from:

<http://guidance.nice.org.uk/TA254/ClinicalAudit/doc/English>

NICE TA254 recommends the development of patient registries for MS to capture long-term treatment-related outcomes.

12. Documents which have informed this policy

See references

13. Links to other policies

This policy follows the principles set out in the ethical framework that govern the commissioning of NHS healthcare and those policies dealing with the approach to experimental treatments and processes for the management of individual funding requests (IFR).

14. Date of review

This policy will be reviewed in April 2016 unless information is received which indicates that the proposed review date should be brought forward or delayed.

References

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Glossary

Term	Meaning
Clinical consensus	General agreement on a clinical/medical subject
Starting and stopping criteria	(In this context).The standards used to find out when a patient could start a certain treatment and stop it
Commissioning	Commissioning in the NHS is the process of ensuring that the health and care services provided effectively meet the needs of the population. It is a complex process with responsibilities ranging from assessing population needs, prioritising health outcomes, procuring products and services, and managing service providers. (Taken from www.dh.gov.uk)
Efficacy	Clinically Effective
NICE	National Institute for Clinical Excellence. NICE is an independent organisation responsible for providing national guidance on promoting good health and preventing and treating ill health. (NICE, 2009)
Prior approval	In this context, when a certain treatment is labelled 'prior approval', it means that before a provider (e.g. a hospital) can give the treatment to a patient, they need to ask the commissioning body for their area to assess and agree to fund it. If the commissioners agree to fund it, then the treatment can be provided to the patient.
Routinely Commissioned	Paid for without prior approval

Version Control Sheet

Version	Section/Para/Appendix	Version/Description of Amendments	Date	Author/Amended by
1	Policy	Update to include use of fingolimod post glatiramer acetate and natalizumab	Feb 14	CRG
2	5	Added evidence base	Feb 14	Malcolm Qualie
3				
4				
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6				
7				
8				
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10				

**Change Notice for Published Specifications and Products
developed by Clinical Reference Groups (CRG)**

Amendment to the Published Products

Product Name

Clinical Commissioning Policy: Disease Modifying Therapies for Patients with Multiple Sclerosis (MS)

Ref No

D04/P/b

CRG Lead

Graham Venables

Description of changes required

Describe what was stated in original document	Describe new text in the document	Section/Paragraph to which changes apply	Describe why document change required	Changes made by	Date change made
	The option of switching relapsing patients from 1 st line glatiramer acetate (GA) to fingolimod (2 nd line). This is currently not approved under NICE Guidance which only supports a switch from beta interferon (BI) to fingolimod.			CRG	March 2014
	The ability to switch patients currently receiving natalizumab who are at a high risk of PML to fingolimod.			CRG	March 2014

