NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA127 Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis

This guidance was issued in August 2007
The review date for this guidance is June 2010

Recommendation

- A review of the guidance should be deferred until the completion of the SURPASS trial which is expected to be in 2013. At this point the review of TA127 and TA32 should be considered together. That we consult on the proposal.

Consideration of options for recommendation:

Options	**Comment**
A review of the guidance should be planned into the appraisal work programme.	There is currently no new pivotal evidence. We therefore believe that a review of TA127 at present would be a poor use of NICE resources. We have identified an ongoing trial (SURPASS trial) that is expected to complete in May 2013 that will address issue of lack of evidence that was raised as a research recommendation in TA127.
The decision to review the guidance should be deferred until the completion of the SURPASS trial	**The review should be deferred until the completion of the SURPASS trial, at which point, a review of TA127 and TA32 will be considered for review together.**
A review of the guidance should be combined with a review of a related technology and conducted at the scheduled time for the review of the related technology.	There are no related technologies with coincidental timelines. Oral cladribine for relapsing–remitting multiple sclerosis is in the early stages of appraisal. An appraisal of fingolimod for relapsing–remitting multiple sclerosis is expected to begin June 2010. Neither cladribine nor fingolimod have a marketing authorisation. Depending on the outcome of the ongoing appraisals it may be appropriate to reconsider this option.

A review of the guidance should be combined with a new appraisal that has recently been referred to the Institute.	No similar appraisals have been recently referred.
A review of the guidance should be incorporated into an on-going clinical guideline.	There is no on-going clinical guideline. It is noted that Clinical Guideline 8 (issued November 2003) is expected to be considered for review in November 2010.
A review of the guidance should be updated into an on-going clinical guideline.*[1]	New evidence is expected May 2013 that could provide substantial new information about clinical (and therefore cost) effectiveness of natalizumab in one of the two populations for which it holds a marketing authorisation.
A review of the guidance should be transferred to the 'static guidance list'.	Not appropriate because new evidence is expected on completion of the SURPASS trial.

Original remit

To appraise the clinical and cost effectiveness of natalizumab in its licensed indications for the treatment of multiple sclerosis, and to provide guidance to the NHS in England and Wales.

Current guidance

1.1 Natalizumab is recommended as an option for the treatment only of rapidly evolving severe relapsing–remitting multiple sclerosis (RES). RES is defined by two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI.

1.2 People currently receiving natalizumab, but for whom treatment would not have been recommended according to section 1.1 of this guidance, should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

Relevant Institute work

Published

[1] See Appendix A on page 10

Management of multiple sclerosis in primary and secondary care (CG8). Issued: Nov 2003. Expected review date: Nov 2010

Multiple sclerosis - beta interferon and glatiramer acetate (TA32). Issued Jan 2002. TA on static list as a result of review conducted Oct 2007.

In progress

Multiple sclerosis (primary-progressive) - fingolimod. Anticipated issue date: TBC

Multiple sclerosis (relapsing-remitting) – fingolimod. Anticipated issue date: June 2011

Multiple sclerosis – cladribine. Anticipated issue date: March 2011

Suspended/terminated

Multiple sclerosis - cannabinoids. Suspended July 2003 pending manufacturer marketing authorisation.

In topic selection

[redacted]

Safety information

Feb 2010. FDA has notified that the risk of developing progressive multifocal leukoencephalopathy (PML) with natalizumab increases with the number of infusions received.

Details of new indications

Drug (manufacturer)	Details
Natalizumab (Biogen)	Phase II for relapsed or refractory multiple myeloma
Natalizumab (Biogen)	Approved in US for Crohn's Disease.
Natalizumab (Biogen)	For MS-related fatigue. Phase IV. Estimated completion date Dec 2010.

Details of new products

Drug (manufacturer)	Details
Alemtuzumab (Bayer)	Phase III
Cladribine (Merck Serono)	Pre-registration filed (UK) Planned UK launch date Q4 2010.
Fingolimod (Novartis)	Pre-registration filed. Planned UK launch date Q2 2011
Daclizumab (Biogen)	Phase II
Laquinimod (Teva)	Phase III.
Teriflunomide (Sanofi-Aventis)	Phase III
Estriol (Adeona Pharmaceuticals)	Phase III

On-going trials

Trial name and contact	Details
Study Evaluating Rebif, Copaxone, and Tysabri for Active Multiple Sclerosis (SURPASS) NCT01058005s	Phase III currently recruiting. Estimated completion date May 2013
The Effects of TYSABRI Treatment on Vaccination Response and Lymphocyte Subsets in Subjects With Relapsing Forms of Multiple Sclerosis NCT536120	Phase IV. Estimated completion date Jan 2010
A Prospective, Open-label, Non-randomized, Clinical Trial to Determine if Natalizumab (Tysabri®) Improves Ambulatory Measures in Relapsing-remitting Multiple Sclerosis (RRMS) Patients "TIMER" Study NCT00871780	Phase IV. Currently recruiting participants Estimated completion date Aug 2011

Biomarkers and Response to Natalizumab for Multiple Sclerosis Treatment (Bionat2) NCT00942214	Phase IV. Estimated completion date Feb 2013.
Impact Study of 2 Therapeutic Strategy for Aggressive Remitting Multiple Sclerosis (IQUALYSEP) NCT01065727	Economic evaluation. Currently recruiting. Estimated completion date Jan 2015.

New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline(R) In-Process and Embase. References from 2006 onwards were reviewed. The results of the literature search are discussed in the 'Appraisals comment' section below.

Implementation

A submission from Implementation is attached at the end of this paper.

The implementation advice shows an upward trend in prescribing natalizumab. There is no information of the difference in prescribing between the RES group and the suboptimal therapy group; therefore it is difficult to know whether technology guidance TA127 is being adhered to.

Equality and diversity issues

There were no equality and diversity issues in TA127.

Appraisals comment:

The marketing authorisation of natalizumab for this indication has not changed since the publication of TA127. Natalizumab has a UK marketing authorisation as a single disease-modifying therapy in highly active relapsing–remitting multiple sclerosis for the following groups of people:

- People with rapidly evolving severe relapsing–remitting multiple sclerosis defined by two or more disabling relapses in 1 year, and one 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'.
- People 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 one relapse in the previous year while on therapy, and have at least nine T2-hyperintensive lesions in cranial MRI or at least one gadolinium-enhancing lesion. This patient group is referred to as the 'suboptimal therapy group'.

The Appraisal Committee in TA127 recommended natalizumab as an option for the treatment only of rapidly evolving severe relapsing–remitting multiple sclerosis (RES). The Appraisal Committee also noted that there was no direct evidence about the clinical effectiveness of natalizumab monotherapy in the suboptimal therapy group, and concluded that the clinical effectiveness of natalizumab in the suboptimal therapy group had not been fully established. 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.

Literature searches identified no newly published randomised controlled trials since the publication of TA127. The SURPASS trial is an ongoing trial that may address the issue that was raised as a research recommendation in TA127. The trial will examine people with relapsing-remitting MS that has been active within the past 12 months and are being treated with natalizumab, glatiramer acetate or interferon beta. The SURPASS trial has an estimated completion date of May 2013.

There are two related technologies for the treatment of relapsing-remitting multiple sclerosis that are being appraised under the single technology appraisal (STA) process; fingolimod and cladribine. Neither drug has a marketing authorisation so the details of the indications are currently uncertain. Oral cladribine for relapsing–remitting multiple sclerosis is in the early stages of appraisal with the first Appraisal Committee meeting due to take place in September 2010. An appraisal of fingolimod for relapsing–remitting multiple sclerosis is expected to begin June 2010 with the first Appraisal Committee meeting scheduled for November 2010.

Key issues

There is no new evidence that could inform a review of TA127 at present. However, in 2013 evidence is anticipated that could inform a key area of uncertainty identified in TA127 (that is, the clinical effectiveness of natalizumab in the suboptimal therapy group). Therefore, it would be appropriate for the consideration of this appraisal for review to be deferred until that pertinent evidence becomes available.

A separate issue is whether it would be appropriate to combine review of TA127 with review of the appraisals of cladribine and/or fingolimod. Since the licensed indications of these two related technologies are currently uncertain and the appraisals are in the early stages, it is uncertain whether the licensed populations would match and whether timelines would coincide. However, combination of reviews may be relevant to consider in the future as more information becomes available.

It is also noted that the positive recommendation of natalizumab as a cost-effective option for the treatment of rapidly evolving severe relapsing–remitting multiple sclerosis was based on the acceptance of beta interferon as the comparator that best reflected current clinical practice. This is in contrast to the guidance on beta interferon and glatiramer acetate for the treatment of

multiple sclerosis (TA 32), which does not recommend the use of beta interferon, and in recognition of the risk sharing scheme that has been set up by the Department of Health.

It should be considered that the review of TA127 should be deferred until the completion of the SURPASS trial, at which point both TA127 and TA32 be considered for review together

GE paper sign off:

Helen Chung, Associate Director – Appraisals, CHTE
June 2010

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NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

IMPLEMENTATION DIRECTORATE

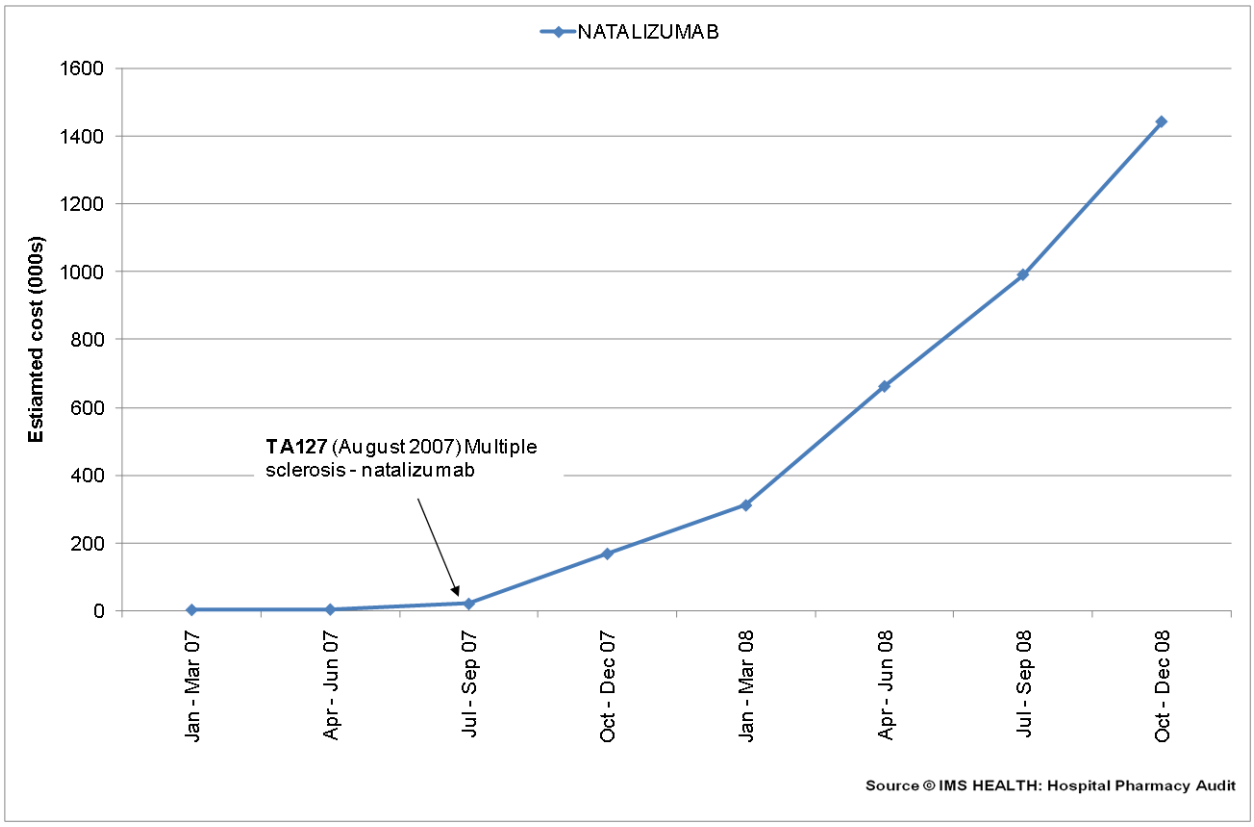
Guidance Executive Review

Technology appraisal 127: Natalizumab for Multiple sclerosis

1. National data

Data showing trends in prescribing costs are presented below. Unfortunately this data does not link to diagnosis so needs to be treated cautiously in relation to the specific recommendations of the guidance. Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

Figure 1 Trend in cost of prescribing natalizumab in hospitals in England



2. External literature

2.1 ERNIE

2.1.1 The Information Centre for Health and Social Care (2009) Hospital Prescribing, 2008: England

http://www.ic.nhs.uk/webfiles/publications/Primary%20Care/Prescriptions/hospre08/Hospital_prescribing_2008_report2.pdf

Cost (£000s)	Primary care	% growth primary	FP10HP*	% growth	Hospital	% growth hospital	Total	% growth total
Natalizumab	**-**	**-**	**-**	**-**	**3,426.1**	**1,547.6**	**3,426.1**	**1547.6**

*FP10HP = prescriptions written in hospitals but dispensed in the community

The data shows that all prescribing for natalizumab is carried out in a secondary care setting.

2.1.2 NHS Information Centre for Health and Social Care (2009) Use of NICE appraised medicines in the NHS in England-Experimental Statistics

Overview

Natalizumab is licensed for use in patients with highly active relapsing-remitting multiple sclerosis despite treatment with interferon beta or those with rapidly evolving severe relapsing-remitting multiple sclerosis. Treatment with natalizumab should be initiated and supervised by a specialist.

Expected Number of Eligible Patients

The following assumptions were used in the calculation of the expected number of eligible patients. The assumptions are taken from data on existing practice, research and the views of experts in the field used in the NICE costing template (for further detail see: http://guidance.nice.org.uk/TA127/CostTemplate/xls/English).

Assumption and Evidence/Source

Assumption	Evidence/Source
Numbers of multiple sclerosis patients eligible for disease-modifying treatments = 9000	HSC 2002/004 Cost effective provision of disease modifying therapies for people with multiple sclerosis estimates an upper limit of 9000 patients in England and Wales eligible for disease modifying therapies, scaled for England only
Proportion of patients assumed to have relapsing-remitting multiple sclerosis = 86%	Palace J, Cooper C, MS risk-sharing scheme monitoring study uptake estimates 14% of multiple sclerosis patients eligible for disease modifying therapies have secondary progressive MS, the remainder have relapsing-remitting MS.
Proportion of patients with rapidly evolving relapsing-remitting multiple sclerosis = 22%	AFFIRM study
Proportion of patients assumed to be appropriate for treatment with natalizumab = 26%	Expert clinical opinion was sought as to the likely proportion of patients who would be switched to natalizumab.

Observed uptake

No use of this medicine was found in community data and so only HPAI data was used.

Results

The NICE costing template expected the annual equivalent of 419 patients giving a predicted use of 152.9 thousand doses per year. The observed use in 2008 was 91.0 thousand defined daily doses, a ratio of 0.6 to 1. Use was increasing over 2008 and if the use in the first quarter of 2009 continued throughout the year then the use in 2009 would be 194.7 thousand DDDs which would give a ratio of 1.3 to 1.

The expected number of eligible patients at SHA level ranged from 21 to 62 patients and so a sub-national analysis is not appropriate.

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The graph below shows national (England) expenditure by quarter since 2007.