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

Premeeting briefing

This briefing presents major issues arising from the manufacturer's submission, Evidence Review Group report and personal statements made by nominated clinical specialists and patient experts. Please note that although condensed summary information is included for ease of reference, this briefing should be read in conjunction with the full supporting documents.

The manufacturer was asked to provide clarification around the clinical evidence from the AFFIRM and SENTINEL trials, details on the use of adverse-event data and meta analysis, data on utility derivation and how the probabilities and structure of the model were decided upon.

Abbreviations

ERG	Evidence Review Group
EDSS	expanded disability status scale
EQ-5D	a standardised instrument for use as a measure of health outcome
HARRMS	highly active RRMS
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IFN-beta	interferon beta
ITT	intention to treat
MRI	magnetic resonance imaging
MS	multiple sclerosis
PML	progressive multifocal leukoencephalopathy
RES	rapidly evolving severe RRMS
RRMS	relapsing–remitting multiple sclerosis
ScHARR	The School of Health and Related Research, University of Sheffield

Licensed indication

Natalizumab (Tysabri, Biogen Idec) has a marketing authorisation as a single disease-modifying therapy in highly active relapsing–remitting multiple sclerosis (HARRMS) for:

- patients with rapidly evolving severe relapsing-remitting multiple sclerosis (RES) (defined as patients with two or more disabling relapses in 1 year, and with one or more gadolinium-enhancing lesions or a significant increase in T2 lesion load on brain magnetic resonance imaging [MRI] compared with a previous MRI)
- patients with high disease activity (defined as at least one relapse in the previous year while on therapy and either at least nine T2-hyperintense lesions or at least one gadolinium-enhancing lesion on brain MRI), despite treatment with an interferon beta (IFN-beta) drug (suboptimal therapy)

Key issues for consideration

- Can the AFFIRM trial be generalised to the population of interest and does it sufficiently represent the suboptimal therapy group?
- Are the RES group and suboptimal therapy group definitions appropriate for guidance to be issued?
- Is the extrapolation of the clinical and economic data reliable and are the conclusions derived from the cost-effectiveness modelling robust?
- Given that the incremental cost-effectiveness ratios (ICERs) are outside the range of cost per quality-adjusted life year that is generally considered cost effective, does the Committee believe there are extenuating circumstances that allow natalizumab to be recommended?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	Adults with highly active relapsing remitting multiple sclerosis who have either: • high disease activity despite treatment with IFN-beta (suboptimal therapy) or • rapidly evolving severe relapsing–remitting multiple sclerosis (RES)
Intervention	Natalizumab 300 mg
Comparators	For adults with suboptimal therapy: • glatiramer acetate, for patients failing on IFN-beta • IFN-beta for patients failing on glatiramer acetate • best supportive care with no disease-modifying treatment For adults with RES: • IFN-beta • glatiramer acetate • best supportive care with no disease-modifying treatment
Outcomes	Mortality, relapse rate, disability progression[a], adverse effects of treatment, including progressive multifocal leukoencephalopathy (PML) and health-related quality of life (HRQoL).
[a] Probability of sustained disability progression was defined as an increase in expanded disability status scale (EDSS) sustained for 12 or 24 weeks at 2 years.	

The scope for this appraisal included mitoxantrone. However, the manufacturer of natalizumab stated that it did not provide a comparison with mitoxantrone because this drug is recommended by a NICE clinical guideline ('multiple sclerosis: National clinical guideline for diagnosis and management in primary and secondary care') for use only within clinical trials and because it is not commonly used outside study settings in the UK.

1.2 ERG comments on the manufacturer's submission

1.2.1 Population

The ERG commented that neither the RES nor the suboptimal therapy group formed the overall study population in a randomised controlled trial of natalizumab monotherapy. In particular, the suboptimal therapy group was

considered by the manufacturer to be analogous to the intention to treat (ITT) population in the AFFIRM study. However, the ERG considered the AFFIRM population to be different from the suboptimal therapy group because the ITT population in AFFIRM had relapsing remitting multiple sclerosis (RRMS), not HARRMS, and was not as extensively treated.

The ERG discussed the potential size of the RES group. The diagnosis of MS may take some time and patients might be prescribed IFN-beta during the diagnosis; they would consequently become part of a possible suboptimal therapy group. Therefore, the actual size of the RES group might be very small.

The ERG commented that the RES and suboptimal therapy groups might not be easily differentiated in clinical practice. The groups are likely to overlap such that a patient who is not diagnosed with RES will be treated with disease-modifying treatments and therefore could eventually join the suboptimal therapy group.

1.2.2 Intervention

The ERG concluded that the intervention was described appropriately.

1.2.3 Comparators

The ERG considered the comparators chosen to be appropriate and that the exclusion of mitoxantrone was appropriate given the restrictions on its use.

1.2.4 Outcomes

The ERG considered the use of expanded disability status scale (EDSS) states to measure disability progression to be logical, but pointed out that issues with limited responsiveness, validity and intra- and inter-rater reliability have been demonstrated with this measure. Other outcomes such as relapse rate were appropriate to include in the analysis.

1.2.5 Timeframe

The ERG agreed that the 20-year time horizon adopted by the manufacturer in the economic analysis was appropriate. This was the same time horizon

used in the previous appraisal of IFN-beta and glatiramer acetate (NICE technology appraisal 32). However there are limited clinical data for natalizumab over this time period and therefore extrapolation was undertaken, which increased the uncertainty in the results. The ERG was unable to estimate the effect of extrapolating the clinical findings to a 20-year time horizon.

1.3 Statements from professional/patient groups and nominated experts

The clinical specialists and patient experts felt that the decision problem was well defined and natalizumab's place in the treatment pathway was clear. However, comments were received on the appropriateness of the choice of subgroups. The suboptimal therapy group was considered to lack a sufficient evidence base from the trials, whereas the RES group appeared to be too restrictive and could have been expanded. The current definition of the RES group would result in limiting the number of patients eligible to a few thousand. There was general agreement that IFN-beta was the most commonly used comparator followed by glatiramer acetate.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

2.1.1 The manufacturer identified four trials that examined the use of natalizumab in MS.

- AFFIRM was a multicentre, multinational, randomised, double-blind, placebo-controlled, parallel-group study (n = 942) that was used to define the RES group (n = 209).
- SENTINEL (natalizumab plus IFN-beta versus IFN-beta alone, n = 1196) was the registration trial for the suboptimal therapy group.
- MS 201 and MS 231; two phase II trials that provided additional data.

In the SENTINEL trial, the natalizumab plus IFN-beta combination was found to increase the risk of fatal adverse events and therefore this combination treatment is excluded from the marketing authorisation. Hence the manufacturer did not present evidence from SENTINEL to provide information in support of the suboptimal therapy group. Instead, the manufacturer assumed equivalence between the suboptimal therapy group and the AFFIRM ITT population for the economic evaluation, which was stated to be a conservative assumption. The manufacturer argued that the suboptimal therapy group represents the RES group at a later point in time and therefore it would be more appropriate to use the RES efficacy data and adjust for age (given that suboptimal therapy patients are further along the treatment pathway and therefore would be older) than the ITT population from AFFIRM.

2.1.2 The results from AFFIRM for the direct comparison of natalizumab with placebo for the ITT population (n = 629 for natalizumab; n = 315 for placebo) and RES (n = 148 for natalizumab; n = 61 for placebo) populations are shown in the table below.

Outcome	**Group**	**Natalizumab (n = 627)**	**Placebo (n = 315)**	**Absolute risk reduction**	**Hazard ratio (95% CI)**
Probability of sustained disability progression (defined as an increase in EDSS sustained for 12 weeks) at 2 years	ITT	0.17	0.29	0.12	0.58 (0.43 to 0.77)
	RES	0.14	0.29	0.15	0.47 (0.24 to 0.93)
Probability of sustained disability progression (defined as an increase in EDSS sustained for 24 weeks) at 2 years	ITT	0.11	0.23	0.12	0.46 (0.33 to 0.64)
	RES	0.10	0.26	0.16	0.36 (0.17 to 0.76)
Annualised relapse rate at 1 year	ITT	0.26	0.81	0.55	0.68 (0.59 to 0.74)
	RES	0.10	0.26	0.16	0.36 (0.17 to 0.76)
Annualised relapse rate at 2 years	ITT	0.24	0.73	0.50	0.68 (0.60 to 0.74)
	RES	0.28	1.46	1.17	0.81 (0.70 to 0.88)

2.1.3 The manufacturer concluded that for both the RES and suboptimal therapy groups natalizumab had a clinically and statistically significant benefit compared with placebo. In addition, a higher proportion of patients who received natalizumab remained disease free (natalizumab 23%, n = 177; placebo 6%, n = 18). Natalizumab was also associated with reduced severity of relapse, with lower rates of steroid treatment (63% versus 73%) and hospitalisation (3.4% versus 9.7%).

2.1.4 Indirect comparisons were carried out between natalizumab and IFN-beta and between natalizumab and glatiramer acetate. These were used to compare the relative efficacy, safety and HRQoL of the interventions. The manufacturer identified one systematic review each for IFN-beta (Rice et al.) and glatiramer acetate (Munari et al.). The manufacturer used the method of Song et al. to compare the trials, the results of which comparison are shown below. It should be noted that the ITT population was used to represent the suboptimal therapy group, and that the effectiveness of IFN-beta and glatiramer acetate was assumed to be the same for the RES and suboptimal therapy groups. It should also be noted that all data for IFN-beta and glatiramer acetate were derived from a RRMS population.

Cochrane endpoints	**AFFIRM endpoints**	**Indirect comparison: natalizumab versus IFN-beta**			
		RR	**lcl**	**ucl**	**P value**
All patients who progressed at 2 years	ITT patients who progressed at 2 years (24 weeks)	[redacted]	[redacted]	[redacted]	[redacted]
	RES patients who progressed at 2 years (24 weeks)	[redacted]	[redacted]	[redacted]	[redacted]
All patients who progressed at 2 years	ITT patients who progressed at 2 years (12 weeks)	[redacted]	[redacted]	[redacted]	[redacted]
	RES patients who progressed at 2 years (12 weeks)	[redacted]	[redacted]	[redacted]	[redacted]

RR relative risk; lcl [lower confidence limit], ucl [upper confidence limit]

Figures in brackets are the length of time the increase in expanded disability status scale (EDSS) was sustained.

Cochrane endpoints	AFFIRM endpoints	Indirect comparison: natalizumab versus glatiramer acetate			
		RR	lcl	ucl	P value
All patients who progressed at 2 years	ITT patients who progressed at 2 years (12 weeks)	[redacted]	[redacted]	[redacted]	[redacted]
	RES patients who progressed at 2 years (12 weeks)	[redacted]	[redacted]	[redacted]	[redacted]
All patients who progressed at 2 years[1]	ITT patients who progressed at 2 years (24 weeks)	[redacted]	[redacted]	[redacted]	[redacted]
	RES patients who progressed at 2 years (24 weeks)	[redacted]	[redacted]	[redacted]	[redacted]
All patients who progressed at 2 years[1]	ITT patients who progressed at 2 years (12 weeks)	[redacted]	[redacted]	[redacted]	[redacted]
	RES patients who progressed at 2 years (12 weeks)	[redacted]	[redacted]	[redacted]	[redacted]
RR relative risk; lcl [lower confidence limit], ucl [upper confidence limit] Figures in brackets are the length of time the increase in expanded disability status scale (EDSS) was sustained.					

2.1.5 Natalizumab demonstrated statistically significantly reduced relapse rates compared with glatiramer acetate and IFN-beta, 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.

2.1.6 The manufacturer presented safety results from AFFIRM that demonstrated that the most statistically common adverse events were fatigue and allergic reaction. The conclusion of this analysis was that natalizumab was not associated with higher incidence of adverse events compared with placebo.

2.1.7 The manufacturer carried out an indirect safety comparison between natalizumab and IFN-beta and glatiramer acetate. Natalizumab statistically significantly decreased the incidence of influenza-like symptoms and myalgia/arthralgia compared with IFN-beta, with risk ratios of 0.47 and 0.68 respectively. There was

[1] Includes Bornstein (1987) study in meta analysis, which was excluded in ScHARR model,

no statistically significant difference in the safety profile between natalizumab and glatiramer acetate.

2.1.8 In up to 4% of patients receiving natalizumab therapy hypersensitivity reactions occurred, which were generally associated with the presence of anti-natalizumab antibodies. Patients who experience these events were to permanently discontinue natalizumab.

2.1.9 Two cases of progressive multifocal leukoencephalopathy (PML) were reported in the SENTINEL study and one case in a separate study of natalizumab in Crohn's disease. Both studies involved concomitant use of immune-modulating drugs, but the manufacturer could not exclude the possibility of an increased risk of PML with natalizumab monotherapy.

2.1.10 The manufacturer presented evidence from 929 patients in the AFFIRM trial that showed that natalizumab led to significant benefit in health-related quality of life compared with placebo as measured by the Short Form-36 utility instrument (see table 21 of the manufacturer's submission). The manufacturer noted that this gain was not demonstrated with the Multiple Sclerosis Quality of Life Instrument; and suggested that this discrepancy was because of the way in which this instrument was constructed.

2.2 ERG comments

2.2.1 The ERG commented that despite the lack of a full systematic review of trials and a robust search strategy, no important trials were excluded from the analysis.

2.2.2 The ERG considered the AFFIRM trial to be well conducted and analysed, and its results for RRMS robust. The post hoc analysis of the use of natalizumab in HARRMS for the RES group seems to indicate that natalizumab achieved similar reductions in outcomes as in the RRMS group.

2.2.3 The ERG noted that no randomised controlled trial has explicitly studied natalizumab in a suboptimal therapy group. Therefore any conclusions about the efficacy of natalizumab in the suboptimal therapy group were the result of extrapolating results from other trials of different populations, which may result in erroneous conclusions. In addition, the use of SENTINEL to derive results is problematic because the comparator was IFN-beta and not placebo.

2.2.4 The ERG considered the indirect comparison carried out by the manufacturer was methodologically suitable given the available data. It noted that the indirect comparison [redacted] The relapse rate did appear to be improved in both populations receiving natalizumab compared with IFN-beta and with glatiramer acetate. Natalizumab significantly improved disability progression at 24 weeks compared with glatiramer acetate.

2.2.5 The ERG considered the adverse events associated with natalizumab, especially the incidence of fatal PML. It noted that the European Medicines Agency recommended a number of conditions for treatment of the RES group because of infection concerns, including PML. The requirements include an escape rule (stopping rule) for non-responders after 6 months of treatment and administration in specialist centres.

2.2.6 The ERG noted that the indirect comparison of the adverse events between natalizumab, IFN-beta and glatiramer acetate was subject to heterogeneity in the reporting and classification of adverse events, which made the outcomes difficult to compare. Compared with glatiramer acetate there was no significant difference in adverse events. Compared with IFN-beta there was a lower

incidence of influenza-like symptoms in patients receiving natalizumab. However, the ERG noted that there was no comparison of the risk of PML and allergic reaction associated with administration of the drug. In the ERG's opinion, an inclusion of these adverse events might cause the ICER to increase.

2.3 Statements from professional/patient groups and nominated experts

2.3.1 The clinical specialists and patient experts both emphasised the importance of extended relapse control and the improvement that it could offer in terms of health-related quality of life. Fewer relapses would mean fewer hospital admissions and reduced administration of steroids to treat relapses. However, specialists commented that some patients would welcome a regular hospital appointment because it would allow regular monitoring, in contrast with current therapies in which self injection appears to be common and hospital monitoring is less frequent. The major concern expressed by both clinicians and patients was the possibility of increased rates of PML. However, there was a consensus that these risks have to be balanced against the benefits of treatments; in comparison with existing treatments the benefits were considered by both clinicians and patients to be far greater.

3 Cost effectiveness evidence

3.1 Cost effectiveness in the manufacturer's submission

3.1.1 The recommendations for the use of IFN-beta and glatiramer acetate made in NICE technology appraisal 32 lead to the Department of Health initiating a risk-sharing scheme for the use of these drugs ('Health services circular 004', 1 February 2002). In this scheme, an ICER for IFN-beta or glatiramer acetate of £36,000 per quality-adjusted life year or below was deemed to be cost effective. The manufacturer of natalizumab argued that £36,000 per

quality-adjusted life year should therefore also be considered cost effective in this appraisal. This assumption had not been discussed with NICE. It should be noted that the ICER used in the risk-sharing scheme is not the responsibility of NICE and that the scheme makes provision for updating any judgements on cost effectiveness '(Health services circular 004', point 46).

3.1.2 The manufacturer did not identify any published cost-effectiveness analysis that compared natalizumab with IFN-beta or glatiramer acetate. It presented a de novo analysis based on a natural history multi-state Markov model. The manufacturer based its economic model on the model constructed by the School of Health and Related Research (ScHARR) at the University of Sheffield for the development of NICE technology appraisal 32. The model included 21 states, which represent patients with RRMS in EDSS 0–9, secondary progressive multiple sclerosis (SPMS) in EDSS 0–9 and death. As in the ScHARR model, the cycle length was 1 year and the time horizon 20 years.

3.1.3 Transition probabilities for underlying progression for RES were derived from the placebo arm of the RES population in the AFFIRM trial. For the suboptimal therapy group, the placebo arm from the ITT population was used as a proxy. The manufacturer also drew heavily on the London Ontario data set, which is a longitudinal study of more than a 1000 patients followed for a mean of 25 years. It categorised patients various stages of the disease, however it did not collect information on RES or suboptimal therapy groups. This data set was also used in the previous ScHARR model.

3.1.4 The manufacturer commissioned a cross sectional study undertaken via a postal survey (UK MS survey 2005), which was distributed by the MS Trust with its newsletter. A total of 2708 people (20.9%) replied and 2048 responses (15.8%) were suitable for analysis. These data was used to assess the resource

requirements of people with MS, health state costs and the utility associated with the disease.

3.1.5 Utilities for each EDSS state were derived from EQ-5D scores collected as part of the UK MS survey. These EQ-5D scores were then fitted to a multivariate regression from EDSS states 0 to 9 for MS patients, in addition to disease type, relapse and year since diagnosis. Disutilities from adverse events for IFN-beta and glatiramer acetate were estimated from published studies; however the manufacturer did not include the disutility from administration of these treatments in its model. The proportions of patients assumed to experience disutility related to adverse events for IFN-beta and glatiramer acetate were 30% and 20%, respectively, which was an assumption used in the first year of the ScHARR model. However, these disutilities were applied for all cycles of the model and not just the first year.

3.1.6 The base case analysis also took into account withdrawal rates and the disutility of carers which was derived from data collected for Alzheimer's disease and the UK MS survey.

3.1.7 The base case results are shown in the following table.

RES group					
Comparison	**Cost per patient (£'000s) (natalizumab)**	**QALYs per patient (natalizumab)**	**Cost per patient (£'000s) (comparator)**	**QALYs per patient (comparator)**	**Incremental cost per QALY gained (£'000s)**
natalizumab versus IFN-beta	162.0	7.51	122.3	6.27	32.0
natalizumab versus glatiramer acetate	162.0	7.51	110.0	6.01	34.6
natalizumab versus best supportive care	162.0	7.51	84.7	5.78	44.6
suboptimal therapy group					
natalizumab versus IFN-beta	159.5	7.58	119.2	6.65	43.4
natalizumab versus glatiramer acetate	159.5	7.58	106.2	6.38	44.3
natalizumab versus best supportive care	159.5	7.58	79.2	6.15	56.1
QALY quality-adjusted life year					

3.1.8 The manufacturer carried out univariate sensitivity analyses for both the RES and suboptimal therapy groups. These analyses demonstrated that the variables that had the greatest effect on the ICER were the baseline characteristics of the model population, the natural history of the disease, the efficacy of disease-modifying treatments, cost, the health economic perspective chosen and time horizon over which costs and outcomes are evaluated (see table 85 in the manufacturer's submission). Overall, the variation in ICERs was less for the RES group than for the suboptimal therapy group. To examine the uncertainty in the data for the suboptimal therapy group, the manufacturer carried out an additional sensitivity analysis on the RES group. In this, the age of the RES population was increased and the efficacy and disability progression rates altered accordingly. In this analysis for the suboptimal therapy

group the ICERs decreased to a range of £32,000 to £35,000. Additionally, the manufacturer altered the efficacy rates of the comparators to represent the plausible (manufacturers' opinion) inference that IFN-beta and glatiramer acetate are not as effective in the suboptimal therapy group. This resulted in the ICERs decreasing to £23,000 and £35,000 compared with IFN-beta and glatiramer acetate, respectively.

3.2 ERG comments

3.2.1 The ERG considered that the approach to the economic analysis was pragmatic and drew heavily on methods used in previous appraisals. Although the economic modelling appeared to satisfy the critical appraisal framework applied by the ERG, there were a number of important factors that increased the uncertainty in the results.

3.2.2 The ERG had concerns about the quality of the data used to populate the model, which could affect the reliability of the ICER. The patient characteristics in the model may not have been applicable to the HARRMS population or the RES and suboptimal therapy groups. This is the case especially when patient characteristics are taken from the UK MS survey, where response bias may have occurred, and the London Ontario data set, which included all MS patients, not only those with HARRMS. Also of concern was the use of data from the AFFIRM trial to populate the model; AFFIRM was a much smaller data set and had a much shorter follow up than the London Ontario data set originally used in the ScHARR model.

3.2.3 The ERG noted the discrepancy in values between the manufacturer's data set and with other data sets, especially in terms of utilities attached to EDSS states. The UK MS survey differs in relation to other published data sets, although a full comparison with the data sets used in the ScHARR model was not

possible. The ERG did accept that this was a treatment area with a lack of good quality evidence to use in a cost-effectiveness analysis.

3.2.4 The ERG was concerned about the calculation of costs because they were based on the UK MS survey. This meant that 1-month or 3-month data were extrapolated to 1 year periods. The ERG was also concerned about the way that the model handled testing for PML, which appeared to make it a cost-saving measure. This did not have a major effect on the ICER, but did raise issues about the accuracy of the modelling. The ERG noted that it is not clear if the drop-out rate applied in the model accurately included the patients developing anti-natalizumab antibodies.

3.2.5 The ERG had concerns about the structure of the manufacturer's model. Firstly, based on the AFFIRM data in the model, patients are allowed to move to improved EDSS states; this is different from the ScHARR model in which EDSS scores were assumed only to worsen over time. However, the ERG was of the opinion that the probabilities for improving health state were higher than expected although it was unable to validate these figures. Secondly, the ERG expressed concern over the assumptions about the effects of treatment on the probability of progression. Currently, when the treatment effect is applied, the probability of progressing is reduced and therefore the probability of staying in the same health state increases. Therefore, given that patients are allowed to move to improved EDSS states in the model, a greater proportion of the treatment cohort being in position to improve in terms of EDSS health states in the next model cycle.

3.2.6 The ERG was particularly concerned that, although the manufacturer's model was based on AFFIRM data, it did not replicate the results seen in AFFIRM: The manufacturer used 3-monthly assessments of EDSS states to underpin disability

progression in the model which may have led to the model predicting higher levels of progression than was observed using the cumulative probability of disability progression after 24 weeks. This could have led to an overestimation of the benefit of natalizumab.

3.2.7 The ERG noted that the manufacturer's model, as had the previous ScHARR model, used a constant treatment effect. All efficacy data were from short term trials and the Group was uncertain how efficacy would vary over a 20 year time horizon. The Group further noted that the indirect comparisons (see section 5.6) were not used in the modelling.

3.2.8 The ERG carried out univariate sensitivity analyses to examine variables not included in the manufacturer's analysis. The only variable that had a noticeable effect was the price of natalizumab, which if lowered by 25% would result in ICERs below levels usually accepted as cost effective.

4 Authors

Prashanth Kandaswamy and Elisabeth George, on behalf of the Committee Chair David Barnett and the Lead Team (Lynn Field, John Cairns).